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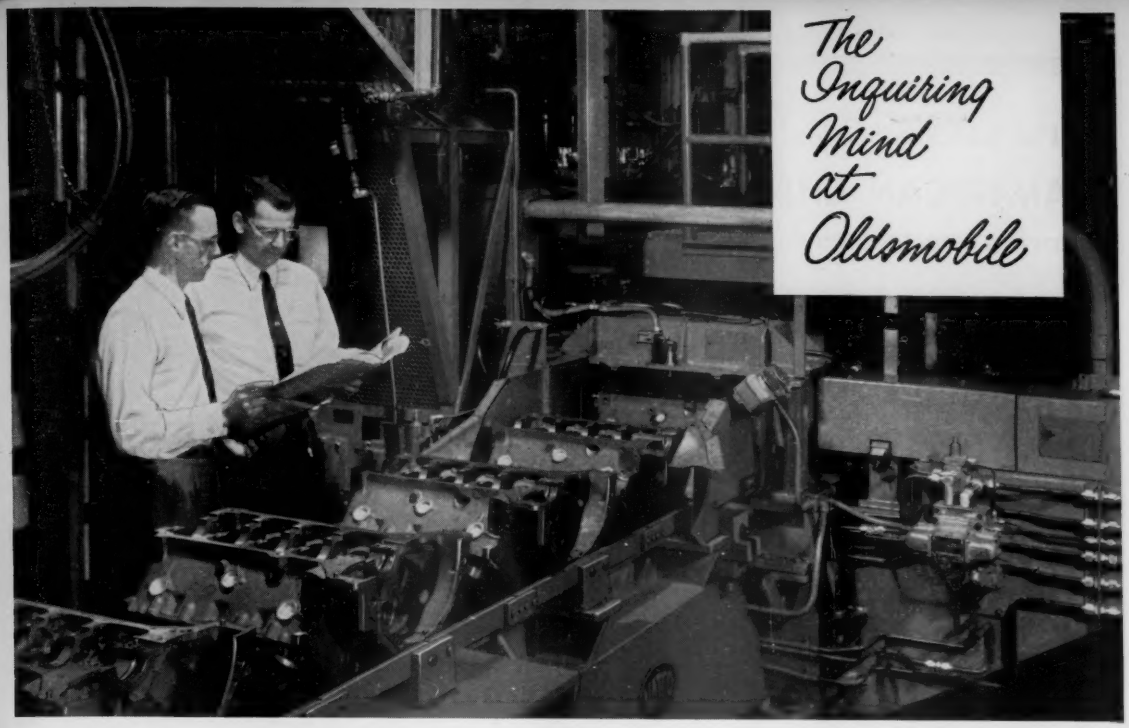

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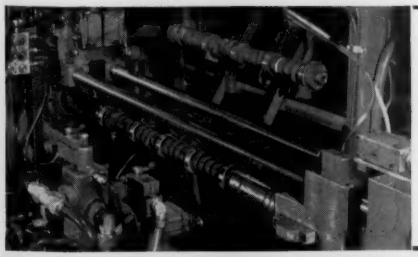

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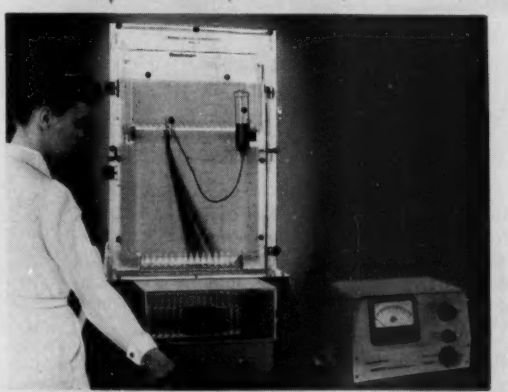

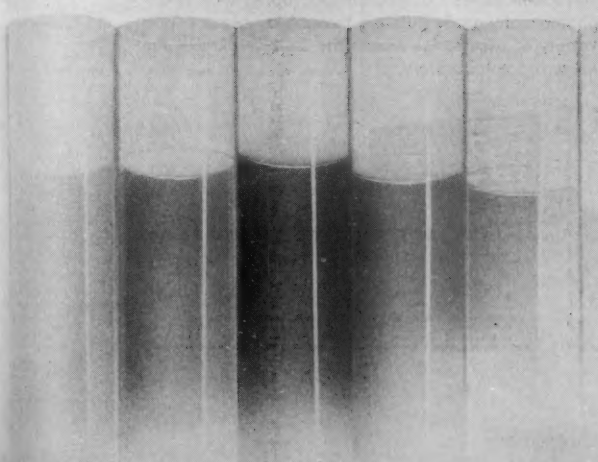

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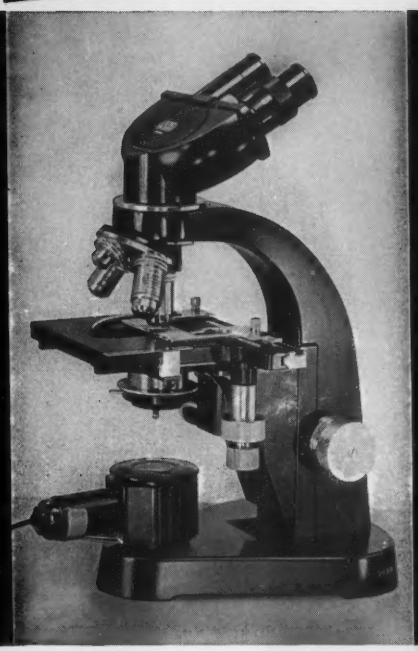

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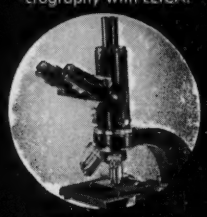

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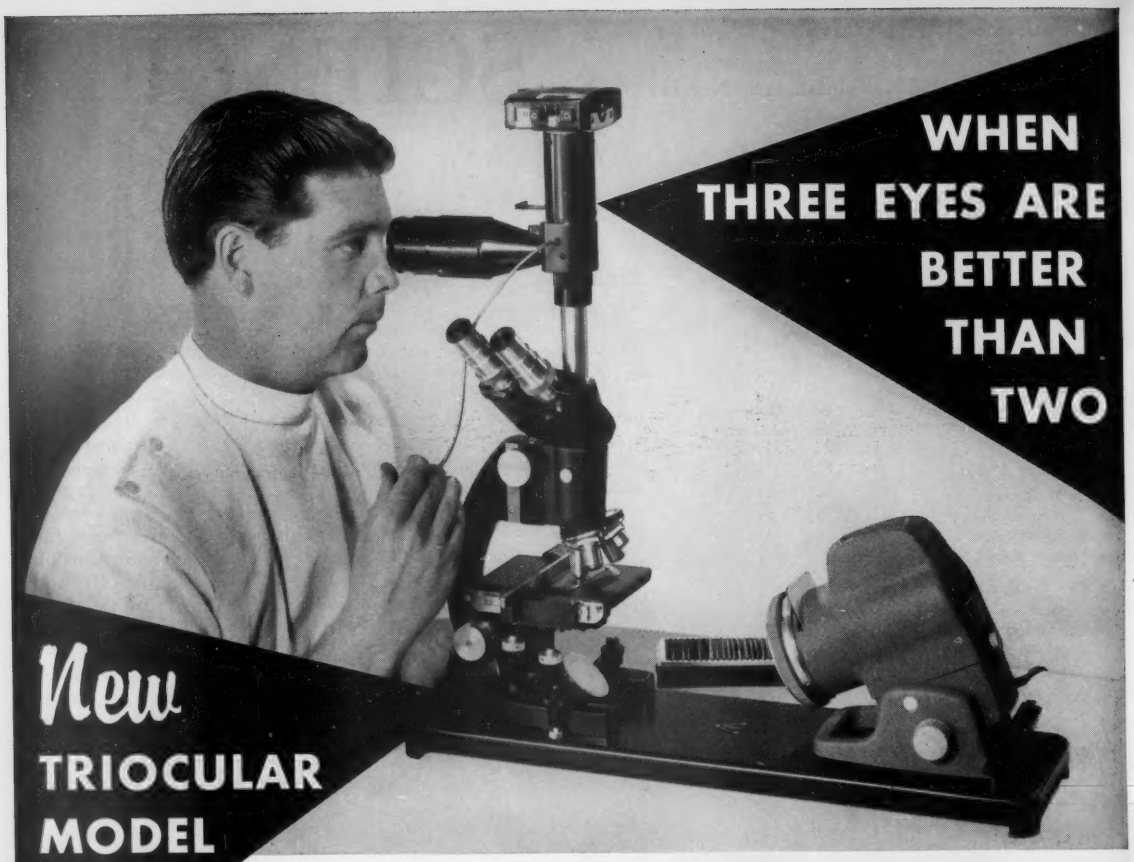
Healthy, Wealthy, and Wise

In the course of the last seven years the appropriations voted by Congress for the National Institutes of Health at Bethesda, Maryland, have increased fivefold, and in each of those years the appropriation voted by Congress has exceeded the amount recommended by the Administration. The 1959 money bill for the Departments of Labor and of Health, Education, and Welfare increases the amount allocated to NIH, excluding that for construction, from the $211.2 million recommended by the Administration, which also happens to be the amount appropriated by Congress for fiscal year 1958, to $294.4 million—an increase of 39 percent. In the preceding years the increase in appropriations over recommendations has varied from 7 percent to 44 percent. With Congress each year topping the Administration, but in widely fluctuating amounts, two questions arise: Upon what kind of thinking is Congress basing its actions? And what can the Administration do to ensure that its budget represents an evaluation, both correct and convincing, of the needs of NIH?

Besides the research conducted within its walls, the National Institutes of Health administers through a system of advisory panels a large program of research grants. One of the arguments for increasing funds that was used this year by the Senate Committee on Appropriations, as set forth in its report, bears on this program. The Committee examined the research grants program for each of the seven institutes as well as for General Research and Service. It found in each case a good number of "approved grants for which there were no funds to provide support." After castigating the Administration for persisting in recommending insufficient budgets, the committee introduced substantial increases down the line.

How much understanding does this examination of the research grant programs show of the procedures generally followed by scientific advisory panels? When faced with a pile of research proposals, such panels generally first separate those proposals that offer some possibilities from those that do not. Then the panel assigns an order of priority to the proposals that are approved, and these are financed off the top as far down as the funds go. This is a perfectly legitimate way for a panel to conduct its business, but it can have misleading implications. From the fact that some approved grants on a given list lack funds, it does not follow that if more money is to be made available to the scientific enterprise, this money must be used to complete the financing of that particular list. On the contrary, it may well be that the additional money should go to other lists or that new lists in other categories should be compiled.

What can the Administration on its part do to increase the chances that its budget expresses, and expresses convincingly, the sums that the various acivities of NIH can best absorb? One suggestion is offered in a recent report on "The Advancement of Medical Research and Education," which was prepared by a board of scientific and administrative consultants for the Department of Health, Education, and Welfare. The report simply calls for the Administration to produce a long-range plan for expanding NIH facilities. It recommends that: "A long-range policy for NIH be worked out promptly as an essential basis for the establishment of sound budgets for the organization." Whatever those budgets should be, it is clear that the chances of arriving at the most advantageous figures will be better if decisions are based upon solid information and foresight. To produce a substantial medical research program requires not only a lot of money but considerable wisdom in its spending.—J.T.



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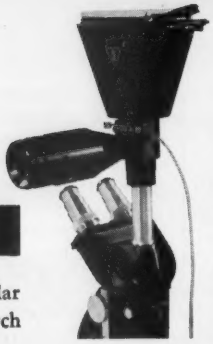

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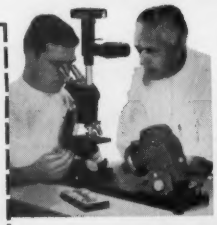

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CURRENT PROBLEMS IN RESEARCH

Ultrahigh-Pressure Research

At ultrahigh pressures new and sometimes unexpected chemical and physical events occur.

H. Tracy Hall

Pressure, defined as force per unit area, is a classical concept. A common unit used in the measurement of pressure is the atmosphere. One atmosphere is equivalent to 14.70 pounds per square inch or to 1.033 kilograms per square centimeter. Natural agencies and man-made devices wherein pressure is deliberately or indifferently generated abound. These pressures cover a tremendous range. For example, the pressure generated by a hand-operated tire pump may be 2 or 3 atm, that generated by a hammer blow may be 5000 atm; a rifle bullet impinging on armor plate, 100,000 atm; conventional explosive shock front, 300,000 atm; and the pressure at the earth's core boundary, 1.4×10^6 atm. Moreover, an "atomic-bullet" from a modern particle accelerator impinging on matter at rest may instantaneously generate 10^{10} atm, while the pressure on the interior of some stars may be as high as 10^{15} atm. Some of the above mentioned pressure generators produce static pressures, while others produce only transitory pressures.

Apparatus

For most experimental work static pressures are necessary. Today's laboratory machines are capable of generating pressures approaching 200,000 atm simultaneously with temperatures of 3000°C and maintaining these conditions for hours.

Progress in high-pressure research is directly dependent on progress in design of high-pressure apparatus. It is appropriate, therefore, to consider some of the problems of apparatus design and some recent developments in that area. The ordinary form taken by a high-pressure device is that of a piston and cylinder. The cylinder is closed on one end, and the sample contained therein is compressed by forcing a piston in the other end. Such a device, with the vital components constructed of cemented tungsten carbides, is capable of generating maximum pressures of 50,000 atm. Cemented tungsten carbides have the highest compressive strength of any available engineering materials in use today. The tensile strength of cemented carbides, however, is very low. Therefore, components such as cylinders, which are subjected to tensile loads in use, must be supported by alloy steel back-up rings or by some other means. The upper limit of 50,000 atm for a piston-and-cylinder apparatus is set by failure of the piston.

Theoretically, tremendous pressures could be reached by a cascading process whereby one piston-and-cylinder device is placed inside the chamber of a larger device, and so on. In such an arrangement the pressure differential between each stage would not exceed the maximum 50,000 atm. In practice, it has not been feasible to carry cascading beyond two stages. The experimental problems encountered in two stages are rather formidable, and at present such devices have been limited in use to the making of pressure-volume measurements at room temperature.

As has been mentioned, the upper limit of pressures obtainable in piston-and-cylinder devices is set by the strength of the best materials of construction currently available. Materials with higher compressive strengths would of course extend the range of any high-pressure device. Current effort in this direction is centered on the improvement of existing cemented carbides and the making of analogous cemented compositions of diamond or cubic boron nitride powders. Since diamond and cubic boron nitride have compressive strengths about three times as great as that of hard metal carbides, research on cemented compositions of these materials seems very worth while.

Apparatus currently available for use at pressures above 50,000 atm (other than the above-mentioned two-stage device) are based on the idea that a multistage effect can be obtained in a "single-stage" device.

P. W. Bridgman, Nobel laureate and long-time pioneer in the field of high pressure, first used this idea in the Bridgman anvil apparatus (Fig. 1). In this device, two cemented tungsten carbide "anvils" oppose each other. The working face of each anvil is the surface of a broad truncated cone. The included angle of a section through this cone is about 170°. The sample to be compressed is made in the form of a thin wafer approximately 0.010 inch thick and 0.375 inch diameter. A 0.500 inch (outside diameter) pipestone ring surrounds the sample. The assembly of wafer, sample, and pipestone ring is compressed between the anvil faces. The pipestone ring acts as a gasket to prevent loss of the sample by lateral extrusion between the anvils. This type of device has been used at pressures approaching 200,000 atm. These pressures are possible because the anvil faces receive "massive-support" from the adjacent carbide—that is, the intense load on

The author is director of research at Brigham Young University, Provo, Utah.

the anvil faces is "fanned-out" throughout the carbide bulk beneath the faces. Some of this load will be tensive and is absorbed by cylindrical steel binding rings which surround the carbide anvils. The relative motion along the anvil line of centers which is necessary to effect compression of the sample is made possible by the remarkable properties of the pipestone (catlinite). This material—a hydrous, iron-bearing aluminum silicate related to pyrophyllite and talc—compresses linearly with the load and at the same time possesses sufficient internal and surface friction to "contain" the sample and prevent its extrusion from between the anvils.

Bridgman anvils have been effectively used in measuring electrical resistances of materials as a function of pressure at room temperature. With external heating they have been used in mineral synthesis problems. The pressures obtainable with external heating must of necessity fall off with increasing temperature because of loss of strength of the carbide. Thus, at 1000°C, the maximum pressure obtainable is reduced to about 20,000 atm.

The massive-support and "motion-via-compressible-gasket" principles have been utilized in a device known as the "tetrahedral-anvil apparatus" (Figs. 2, 3, and 4). This equipment provides a larger working volume than the Bridgman anvils and in addition provides for internal heating and entrance of electrical leads for use in making temperature and other measurements. At this writing this device has been used at pressures as high as 130,000 atm. The arrangement for internal electrical-resistance heating allows for temperatures of 3000°C to be maintained at the higher pressures for periods of several hours.

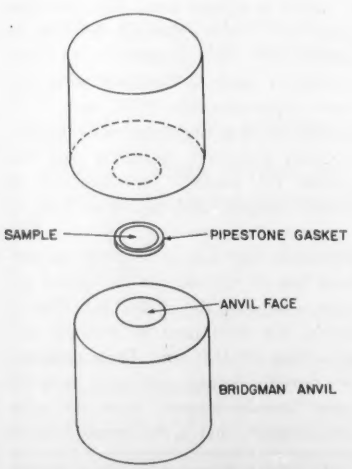

Fig. 1. Bridgman anvils.

Fig. 2. Details of tetrahedral anvils.

In the tetrahedral-anvil apparatus, four cemented tungsten carbide anvils (Fig. 2) are driven together by hydraulic rams along center lines normal to their triangular faces. These center lines intersect at tetrahedral angles in the center of a regular tetrahedral volume enclosed by the anvil faces. The carbide anvils are surrounded by steel binding rings that absorb the tensive loads. In this device, a regular, pyrophyllite tetrahedron (Fig. 3), the edges of which are 25 percent longer than the corresponding edges on the triangular anvil faces, serves as pressure-transmitting medium and as thermal and electrical insulation and also provides the necessary compressible gasket. The sample container, a tube which also serves as the electrical-resistance heater, is located within the pyrophyllite tetrahedron and runs diagonally from opposite edges as is shown in Fig. 3-I. Electrical connections are made to the sample tube (*C*, Fig. 3-II) through metal tabs shaped as shown in cross section at *B* (Fig. 3-II). These tabs are spot-welded to the ends of the metal tube *C*, thus sealing in the contents. The metal tabs from each end of the sample tube make electrical contact with the faces of a pair of anvils which bring in the heating current. Prisms of pyrophyllite (*A*) provide thermal insulation at the ends of the sample container. A thermocouple (*E*) is spot-welded to the sample container, and the leads are brought out through edges of the tetrahedron as shown. Friction of the pyrophyllite on the fine wires is sufficient to hold them in place during high-pressure operation.

In operation, the pyrophyllite tetrahedron is centered on the anvil faces. The anvils are then simultaneously forced together. Since the triangular faces of the pyrophyllite tetrahedron are larger than the triangular anvil faces, some pyrophyllite is forced between the sloping sides of the anvils, and a gasket is automatically formed. Continued motion of the anvils compresses the gasket and tetrahedron, and consequently, the sample.

Pressure calibration of this device is based on locating the hydraulic ram load required to cause certain known abrupt changes in electrical resistance to occur in materials such as bismuth, barium, and thallium.

Some General High-Pressure, High-Temperature Considerations

The concept of pressure is clear-cut when one is dealing with a continuous fluid medium but becomes somewhat hazy when atomic phenomena are involved. For example, 1 mole of helium gas at 0°C, when confined to a volume of 22.4 liters, exerts a nominal pressure at 1 atm on the containing walls. According to kinetic theory, this pressure is generated by molecules of gas rebounding from these walls. At any instant, however, the fraction of the total wall area covered by rebounding helium atoms is only about 0.013 percent. Therefore, the instantaneous average pressure per helium atom generated at the point of contact on rebound is approximately 7500 atm.

Pressure, like temperature, is an intensive property, and when it is multiplied by a capacity factor, an energy is

obtained. When temperature is introduced into a system, the corresponding capacity factor is, of course, the specific heat. When pressure is applied, the corresponding capacity factor is the volume, and the integral

$$\int P dV$$

gives the energy introduced into the system by the pressure.

Pressure and temperature are opposites in their general effect upon matter. Increasing temperature tends to "loosen" systems and increase their entropy, whereas increasing pressure tends to densify systems and decrease their entropy. A solid at low temperature will, upon heating, successively change its crystalline structure, become a liquid, a gas, and then proceed through molecular dissociation to electronic ionization. On the other hand, a gas, when it is subjected to progressively higher pressures, may be condensed to a liquid, various solid phases, and then, when the atoms are in closest packing, proceed through various electronic rearrangements, and finally, at pressures of billions of atmospheres, atoms may be brought within the critical distance of 10^{-13} centimeter at which nuclear fusion may occur.

The profundity of the changes that can be produced in a quantity of matter by injection of energy is qualitatively related to the magnitude of the intensive factor for the type of energy concerned. Heat energy is a type of energy that man has deliberately applied for ages to effect transformations in materials. Temperatures of 1000° to 1500°C, readily obtainable in flames and furnaces, introduce energies of order of magnitude 10 kilocalories. These energies correspond to the ordinary energies of chemical bonds; hence, interaction of this heat energy with matter will produce atomic and molecular rearrangements.

What magnitude of pressures corresponds, in energy, to temperatures of 1000° to 1500°C and, hence, might be expected to produce changes in scope and magnitude comparable to those that are produced by these temperatures? For condensed systems—that is, liquids and solids (gases are not generally interesting because large energy changes may be involved in which the only effect is that of producing a large change in the volume)—corresponding pressures would be of the order of 100,000 to 200,000 atm. In energy, 1 cubic centimeter kiloatmosphere is equivalent to 12.19°K (where degrees are equal to the energy divided by the Boltzman constant k.).

Two problems confront the scientist who is concerned with the transformation of matter from one chemical or physical state to another. The first of these is the thermodynamic problem, and the second concerns the rate of reaction, transition, change, and so on. The thermodynamic equations give information concerning the possibility of transformation from one state to another under certain conditions of temperature, pressure, external fields, and so forth. The rate equations give information concerning the time required for the equilibrium dictated by the thermodynamics to be obtained.

Application of thermal energy to systems to obtain proper thermodynamics and rates for the production of desired changes has been widespread. However, the use of pressure to effect such changes has been quite limited. The use of pressure and temperature together as "levers" to manipulate systems (thermodynamically and rate-wise) to obtain a desired result offers far greater possibilities than the use of either alone. In fact, many transformations (graphite → diamond, for example) can only be brought about by application of the two types of energy.

The general diametrically opposite behavior of pressure and temperature has been mentioned. This carries, generally, into the realm of reaction rates. Whereas rates of reaction are increased by increasing temperatures, increasing pressures decrease the rates. Consequently, it becomes very desirable to have apparatus available that can produce high pressures and high temperatures simultaneously.

Synthesis of Diamond

For almost 100 years great impetus has been given to high-pressure research by the desire to synthesize diamonds. Success in this field has been very elusive. Evidence that the goal has finally been attained, however, is abundantly available in the many diamond grinding wheels now in use for which the wheel's diamond powder was made by the General Electric Company's Metallurgical Products Division. General Electric announced in October 1957 that 100,000 carats of diamond powder had been made as of that date and that they expected to manufacture over a million carats during 1958. The current price of the man-made diamond grit is $3.48 per carat, whereas the price of natural material is about $2.80 per carat. The 24 percent higher price for man-made diamonds is not a deterrent to their use, however, because extensive tests have shown that the grinding efficiency of the man-made diamonds exceeds that of natural diamonds by 35 percent. Diamonds large enough for use as gems have

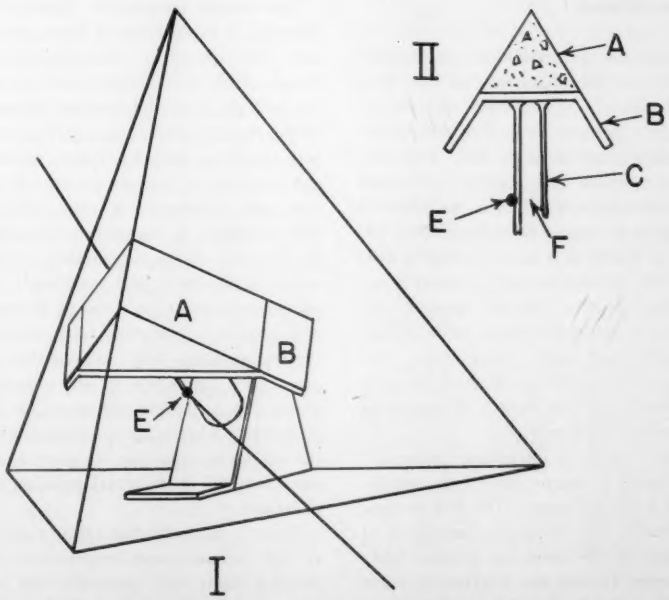

Fig. 3. (I) Details of pyrophyllite tetrahedron with diagonal edge-to-edge heater-and-sample tube. (II) Details of heater-and-sample tube.

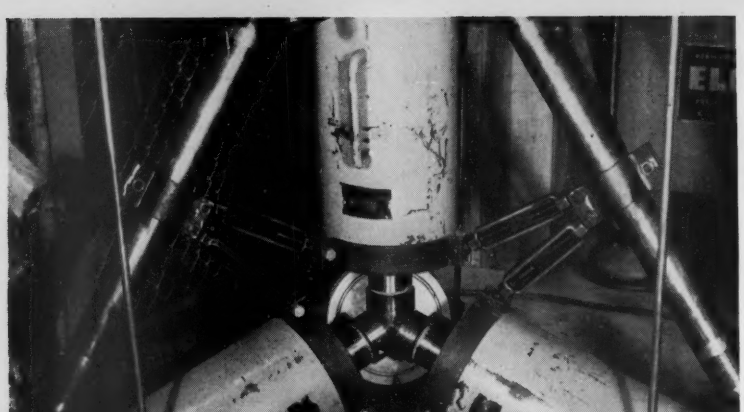

Fig. 4. Tetrahedral anvil apparatus.

not been synthesized up to the present time.

It has not been possible to disclose the details of the methods used to synthesize diamonds because of a government security classification on the patent applications. However, it is generally known that the synthesis is effected by pressures near 100,000 atm and temperatures near 2000°C.

Other Minerals

Naturally occurring high-pressure minerals other than diamond that have been synthesized in recent years include the garnets: pyrope, andradite, almandite, spessartite, grossularite, and uvarovite. These garnets are readily synthesized from the metallic oxides in the presence of water at pressures ranging from 20,000 to 35,000 atm at temperatures near 1000°C. In addition to the naturally occurring garnets, several garnets unknown in nature have been made at high pressure and high temperature. The value of laboratory synthesis of minerals in elucidating the nature of geological processes is self-evident.

Two extremely interesting "minerals" not found in nature have been synthesized in the laboratory. The first of these is Coesite. The chemical composition of Coesite is the same as quartz—SiO_2. However, Coesite has a refractive index of 1.6 and a density of 3.0, whereas the corresponding quantities for quartz are 1.5 and 2.7. In addition, Coesite is remarkably stable toward long heating in hydrofluoric acid. Coesite is readily formed from quartz or other silicates at pressures of 35,000 atm and temperatures of 750°C in the presence of mineralizers such as water, diammonium phosphate, or boric acid. Coesite has been synthesized directly from quartz without the aid of a mineralizer at pressures of 90,000 atm and temperatures of 2000°C.

The second remarkable "mineral" is Borazon, a cubic form of boron nitride with the chemical composition BN. Boron nitride is isoelectronic with graphite, and the normal hexagonal form—a white, slippery solid—has a crystal structure similar to that of graphite. Borazon can be prepared at pressures near 65,000 atm and temperatures near 1500°C. This material is completely analogous to diamond. It is comparable to diamond in hardness and apparently has properties superior to those of diamond with regard to oxidation, resistance and thermal stability. The material thus far prepared is comparable in size to the diamond grit being manufactured for use in grinding wheels. No doubt this material will eventually take its place alongside diamond in industrial grinding applications.

There is no doubt that future research at high pressures and temperatures will produce many new materials that will possess new and useful properties.

Many materials synthesized by the use of high pressure and high temperature are thermodynamically unstable at room temperature and atmospheric pressure. Diamond, a remarkably stable substance from a practical standpoint, is the supreme example of this type of phenomenon, for it is unstable with respect to graphite by some 450 calories under ordinary conditions. Such thermodynamically unstable materials whose rate of transformation to a stable form under ordinary conditions is infinite in terms of human experience are referred to as being metastable.

Metastable materials that become stable under high-pressure conditions can be synthesized in the laboratory by the following sequence of events: (i) subject the starting material to high pressure; (ii) while maintaining pressure, subject the material to a temperature sufficiently high to obtain a reasonable rate of transition or reaction (the pressure and temperature must be such that the metastable end-product desired is stable); (iii) decrease the temperature to room temperature; and (iv) decrease the pressure to atmospheric. Step iv, of course, removes the end-product from stable conditions and subjects it to unstable conditions. However, the temperature had been reduced in step iii so that a material possessing metastability would not revert to the stable form at the completion of step iv. Now, in nature's high-pressure laboratory, this sequence is rarely followed. As materials are brought from the depths of the earth, where they were under high-pressure, high-temperature conditions, pressure and temperature fall together and materials that may have been stable at depth will revert to the unstable form as they rise to the surface. Rare as the diamond is, it is a marvel that it exists at all.

Independent control over pressure and temperature in the laboratory gives man the opportunity to synthesize many things not found in nature.

Interior of the Earth

An indirect investigation of the interior of the earth has become possible with the advent of high-pressure, high-temperature apparatus. Man's direct access to the earth's interior is, of course, very limited. Personal excursions can be made to depths of about 1 mile, this being the depth of the deepest mines. Oil wells have been drilled to depths of 4 miles, and the drill cores and readings from instruments lowered in

the holes yield information concerning these depths. A pressure of 130,000 atm corresponds to a depth of about 260 miles. There is some uncertainty about the temperatures at these depths; but they very likely do not exceed the temperatures now simultaneously obtainable with pressure in the laboratory.

It is probable that some of the seismic discontinuities within the earth are due to the presence of phases not known, under ordinary conditions, to be existent at the earth's surface. For example, it has recently been postulated that the core of the earth is not composed of iron-nickel as is usually assumed, but instead is essentially olivine, which, at the tremendous pressure of 1.4×10^6 atm existing at the core boundary, has been converted to a metallic material of density near 10. Support for this theory is found in the fact that the two smallest planets in the solar system, Mars and Mercury, do not have a core. Calculation shows that these planets are not large enough to maintain the pressure of 1.4×10^6 atm necessary to support the core, even at their centers.

Pressures required to test this postulate are out of reach of present-day apparatus. However, metallic and nonmetallic forms of some elements are known. Gray tin is nonmetallic and has a density of 5.75. Application of pressure to this material transforms it to a metallic white variety of density 7.28. Arsenic is known both as a low-pressure nonmetallic material of density 2.0 and as a high-pressure metallic substance of density 5.73. Phosphorus has a low-pressure yellow form of density 1.82 and a high-pressure black form of density 2.70.

In this same connection, calculations have shown that hydrogen should transform to a metal at pressures beyond 400,000 atm and that $NH_3 + \frac{1}{2}H_2$ should become metallic at pressures beyond 200,000 atm. In such phenomena, pressure is affecting the electronic structure. Such effects offer exciting prospects for future high-pressure research. Since the chemical behavior of an element depends on its particular electronic configuration, gross disruption of this configuration by extremely high pressures could cause the element to behave quite differently. In effect, from a chemical standpoint, extremely high pressures could create a new periodic table.

The melting temperature of a substance is considerably altered by application of high pressure. For example, the melting point of germanium, which is 936°C at 1 atm, is depressed to 360°C (a change of 576°) by a pressure of 180,000 atm. Of course, germanium is an exception to the general rule that the melting point increases with pressure. High pressure has increased the melting point of some refractory materials by well over 1000°C. This fact makes it possible to work at higher temperatures at high pressures than would be possible at 1 atm (provided that the refractory insulation material surrounding the sample is subjected to high pressure, as it is in the tetrahedral anvil apparatus). As a matter of fact, it is quite possible to work with a "liquid" refractory under high-pressure conditions. A substance can flow only if it contains holes into which molecules can move. At pressures exceeding 100,000 atm the number of holes in a molten refractory can be severely reduced. Consequently, the material will be extremely viscous.

Work on the melting points of substances at high pressures has considerable significance in that it should throw some light on the old question about the possible existence of a critical point between liquid and solid which is analogous to the critical point between a gas and a liquid. Furthermore, since melting seems to be a phenomenon in which holes are introduced into a solid, and, since pressure has a strong influence on hole concentration, such studies should aid in obtaining a better understanding of the melting process.

Metallurgy

Metallurgy is an area in which "heat-treatment" has been extensively used to produce alloys with desired physical properties. The heat-treatment has of course been carried out at atmospheric pressure. Now many unsuspected solid phases exist under high-pressure conditions. For example, where only one phase of bismuth exists at 1 atm, eight phases are known in the area bounded by 130,000 atm and 500°C. The existence of additional solid phases, plus the fact that solubilities are greatly affected by pressure, offers exciting possibilities for the use of "pressure-treatment" in addition to heat-treatment in the metallurgy field.

The calculated yield strengths of many metals are 100 to 10,000 times greater than those measured. Yield strength is a structure-sensitive property—that is, the strength is dependent on the existence or nonexistence of vacant sites, dislocations, small and large-angle boundaries, and other factors. The elimination of the above-mentioned structures would result in an improvement of the yield strength of metals. Such an elimination would produce a decrease in volume of the material; and, since the application of pressure tends to drive processes in the direction of decreasing volume, such application might prove beneficial. There are undoubtedly activation (rate) barriers opposing the removal of the above structures. These barriers could be reduced by use of high temperature and catalysts (fluxes) in order to carry out the eliminations at a reasonable rate.

Most materials are polycrystalline. This is another factor causing lower than calculated yield strengths. Of course, a given weight of a single crystal would occupy a smaller volume than the same weight of polycrystals, since the density of the grain boundaries is about 10 percent less than that of the grains (crystals). There is also a certain amount of free energy associated with the grain boundaries. Application of high pressures would favor the elimination of grain boundaries and the growth of single crystals from polycrystals.

Electrical Conductivity

Pressures of 100,000 atm increase the electrical conductivity of most metals by about 20 percent. However, the conductivity of some metals is increased by as much as 400 percent. This phenomenon, of course, is in accord with the general fact that high pressure behaves similarly to low temperature. This raises the question: Is room-temperature superconductivity possible at sufficiently high pressure?

Conclusion

Research at ultrahigh pressures offers many possibilities in many disciplines for obtaining solutions to old problems and for the observance of new phenomena. Only a few possibilities have been suggested here. One thing is certain: in the ultrahigh-pressure field, there are vistas on the horizon.

Oxidative Phosphorylation

Experiments with fragments of mitochondria offer new information about respiratory energy conversion.

Albert L. Lehninger, Charles L. Wadkins,
Cecil Cooper, Thomas M. Devlin, James L. Gamble, Jr.

Oxidative phosphorylation is a vital process in the economy of aerobic cells, probably accounting for over 90 percent of all the adenosine triphosphate (ATP) generated from adenosine diphosphate (ADP) and phosphate at the expense of the energy liberated during catabolism of foodstuffs. Despite the great importance of this process and 20 years of intensive investigation, the enzymatic details of oxidative phosphorylation are still essentially unknown. It is certain, however, that during the exergonic passage of a pair of electrons from substrate to molecular oxygen, via the pyridine nucleotides, flavoprotein, and the cytochromes, 3 moles of ATP are generated in coupled reactions occurring at three points in the respiratory chain (*1–3*), presumably those shown in the upper portion of Fig. 1.

Both electron transport and oxidative phosphorylation take place in mitochondria, the structure of which must be relatively intact in order that oxidative phosphorylation may be observed in vitro. This finding has greatly limited the experimental approaches to the enzymatic mechanisms involved; it is largely for this reason that the mechanism of oxidative phosphorylation remains one of the most conspicuous mysteries in contemporary biochemistry.

In the last three years we have studied experimental procedures for making morphologically less organized preparations from rat liver mitochondria with which the enzymatic details of oxidative phosphorylation could be more directly studied, with the ultimate goal of resolving the mechanism of oxidative phosphorylation by enzyme separation and reconstruction approaches. We have found it possible to obtain fragments of the mitochondrial membrane which contain relatively intact respiratory chain assemblies, including the enzymes necessary for coupling phosphorylation to electron transport. This article summarizes the chemical and enzymatic properties of these membrane fragments, prepared by the action of digitonin on rat liver mitochondria, and the new information they have yielded concerning the mechanism of oxidative phosphorylation and its relation to other aspects of mitochondrial physiology.

Membrane Fragments

Preparation. Washed rat liver mitochondria are suspended in 0.05*M* sucrose and treated in the cold with an 0.8-percent solution of recrystallized, metal-free digitonin. The mitochondria undergo virtual dissolution, leaving a turbid brown solution which is centrifuged at 50,000 *g* for 25 minutes. The supernatant fluid, which is not clear but contains a gelatinous material, is then centrifuged at 100,000 *g* for 25 minutes to sediment the phosphorylating membrane fragments (*4, 5*). When suspensions of this preparation are incubated aerobically with D-β-hydroxybutyrate, ADP, and orthophosphate, oxygen is taken up, acetoacetate accumulates in equivalent amounts, and inorganic prosphate (P_i) disappears with equivalent formation of ATP. The observed P:2*e* ratios (moles of P_i taken up per pair of electrons transferred) have been as high as 2.8 [maximum expected, 3.0 (*2*)] but are more usually in the range 1.7 to 2.3. The addition of Mg^{++} to the test medium is not required for phosphorylation; however, the fragments contain a considerable amount of bound Mg^{++} (*4*).

Approximately 10 percent of the total nitrogen of the starting mitochondria is ordinarily recovered as the active digitonin preparation. Measurements of specific activity (micromoles of acetoacetate formed per milligram of N per minute) indicate that 40 to 60 percent of the total oxidative activity of the original mitochondria is recovered; the particles are thus from four to six times more active per milligram of N than the original mitochondria (*4, 5*).

Oxidative reactions in membrane fragments. These submitochondrial preparations do not catalyze the organized reactions of the Krebs tricarboxylic acid cycle or the fatty acid oxidation cycle. Only D-β-hydroxybutyrate and succinate, among a wide variety of substrates tested, yield significant rates of O_2 uptake. Fragmentation of the mitochondria with digitonin thus does not produce miniature replicas of intact mitochondria, but rather particles containing relatively intact assemblies of enzymes capable of phosphorylating electron transport, which are largely free of substrate-level enzymatic apparatus (*4*). The digitonin fragments are thus strikingly different from the phosphorylating submitochondrial preparations more recently described by Ziegler *et al.* (*6*) and Kielley and Bronk (*7*), which retain much more enzymatic organization on the substrate level.

On the other hand, the digitonin fragments do retain the characteristic organization of the respiratory chain of intact mitochondria. Difference spectra (*4, 5*) show the presence of cytochromes *a*, a_3, *b*, and *c* in the ratio 1.0:1:0:0.7:1.8, which is approximately that observed by Chance and Williams in intact liver mitochondria (*3*). Also present is an enzymatically reducible flavoprotein with the same absorption characteristics as that in intact mitochondria; its molar ratio to the cytochromes is slightly lower. Diphosphopyridine nucleotide (DPN) is present in a bound form which is highly reactive with the bound D-β-hydroxybutyric dehydrogenase but inactive with bound L-malic dehydrogenase, indicating the specificity of physical organization of the respiratory chain. Intact rat liver mitochondria contain some 30 to 40 moles of DPN per mole of cytochrome *a*; the membrane fragments contain less than 1 mole of DPN per mole of cytochrome *a*. Since the specific activity for oxidation of β-hydroxybutyr-

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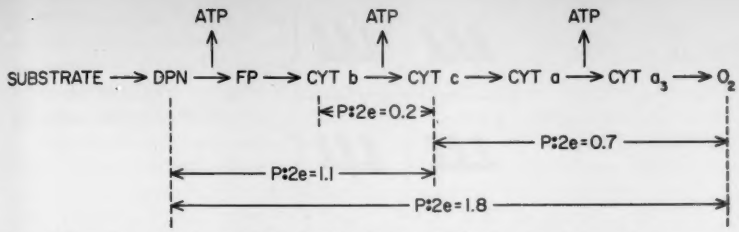

Fig. 1. Respiratory chain and phosphorylation sites. Probable sites of coupled phosphorylations along chain are shown (*2, 3*), as well as experimentally observed values for P:2*e* ratios of different portions of respiratory chain for digitonin particles.

ate in the fragment is fivefold greater than that of intact mitochondria, the bound DPN of the fragment is obviously far more active than the total DPN pool of intact mitochondria. The bound DPN of the membrane fragments is not discharged by phosphate, whereas most of the DPN of intact mitochondria is displaced on such treatment. These facts suggest that most of the DPN in intact mitochondria, although reducible by β-hydroxybutyrate, may be different in location and reactivity from that immediately associated with the respiratory chain. Observations on the kinetics of oxidation and reduction of the total pyridine nucleotide pool in intact mitochondria thus do not necessarily represent the behavior of the bound DPN which is immediately reactive with flavoprotein.

Oxidation of β-hydroxybutyrate in the membrane fragments may be completely inhibited by antimycin A, Amytal, and cyanide; spectrophotometric tests indicate that the pattern of inhibition is identical with that observed in intact liver mitochondria (*5*). However, *added* reduced DPN ($DPN_{red.}$) is oxidized by the preparations through a pathway largely insensitive to antimycin A; little or no phosphorylation is observed (*4*). Added reduced triphosphopyridine nucleotide ($TPN_{red.}$) is oxidized only if DPN is also provided; direct tests showed that the preparations contain a TPN-DPN transhydrogenase (*5*).

The preparations contain bound copper (*8*) and about six times as much iron as can be accounted for by the content of known cytochromes (*5*). Some of the noncytochrome iron may be associated with a pigment believed to be similar to the recently described "mitochrome" (*9*); it exhibits an absorption peak at 426 to 428 mμ in the presence of dithionite, but not with β-hydroxybutyrate. The reduced mitochrome peak of the digitonin particle can, however, be produced enzymatically by the combination of D-β-hydroxybutyrate *plus* succinate (*5*).

Phosphate acceptor specificity. Adenosine diphosphate is the specific phosphate acceptor in the coupled phosphorylations observed with the membrane fragments. The 5′-diphosphates of uridine, cytidine, guanosine, and inosine are completely inactive; they have no stimulatory or inhibitory effect on the action of ADP. Adenosine triphosphate was the sole product of phosphorylation of ADP observed by chromatographic analysis (*4*). The preparations contain little if any myokinase activity (*4, 10, 11*).

Phosphorylation sites. All three phosphorylation sites in the respiratory chain contribute to the over-all P:2*e* ratio during oxidtion of β-hydroxybutyrate by the digitonin fragments. The reduction of cytochrome *c* by β-hydroxybutyrate proceeds with a maximum P:2*e* ratio of about 1.1 (*12*) and the oxidation of reduced cytochrome *c* by oxygen with a maximum P:2*e* ratio of about 0.7 (*13*). When succinate is used to reduce cytochrome *c*, the maximum P:2*e* ratios observed are about 0.2 (*14*) (see Fig. 1). These findings suggest that in the digitonin fragments the phosphorylation site presumed to exist between DPN and flavoprotein is about 90 percent effective, that between cytochrome *b* and *c* about 20 percent, and that between cytochrome *c* and oxygen about 70 percent effective in the average digitonin preparation. These data indicate that there is some selectivity in inactivation of the three coupling mechanisms during preparation of the fragments.

Action of uncoupling agents. Oxidative phosphorylation in the membrane fragments is uncoupled by 2,4-dinitrophenol, Dicumarol, pentachlorophenol, gramicidin, arsenate, and methylene blue with about the same effectiveness shown by these agents in intact mitochondria (*4*). However, the very striking observation was made that two agents known to uncouple phosphorylation in intact mitochondria had absolutely no uncoupling action on the digitonin fragments, even in very high concentrations—namely, Ca^{++} and thyroxine and its analogs (*15*). Thus it appears that these agents have no direct action on the enzymes involved in oxidative phosphorylation, a finding which led us to examine other mechanisms by which thyroxine acts on respiration. Such experiments (*15–18*) have revealed that thyroxine greatly increases the rate of passive swelling of mitochondria by interfering with some aspect of the structure of the membrane. Dinitrophenol, on the other hand, inhibits mitochondrial swelling and antagonizes the effect of thyroxine, clearly demonstrating a fundamental difference in the action of these two agents on mitochondria. These findings have led to an interpretation of the mode of action of thyroxine which is rather different from a simple uncoupling action on oxidative phosphorylation such as is shown by dinitrophenol (see *17, 18*).

Chemical and physical nature of membrane fragments. The digitonin preparations contain about 65 percent protein, about 28 percent phospholipid, and 1 to 2 percent cholesterol. The preparations also contain about 5 percent bound digitonin (*5*).

Ultracentrifugal analysis shows the particles to have an average sedimentation constant of about $S_{w,\ 20°} = 200$. The particles are obviously polydisperse since the sedimenting boundaries spread rapidly. While the material is too crude for exact measurements, an average particle weight of 40 million is suggested as a very gross approximation. When the preparation is subfractionated by differential ultracentrifugation and the separate fractions are tested for activity, all fractions are found to be approximately equal in specific oxidative activity per milligram of N, and the P:2*e* ratio is essentially constant, indicating that the digitonin particles are enzymatically homogeneous but differ in size (*5, 19*). Preliminary electron microscope observations suggest that the digitonin particles are fragments of the mitochondrial membrane, a view confirmed by Siekevitz and Watson (*20*). These considerations suggest that the respiratory enzyme assemblies are more or less evenly distributed throughout the mitochondrial membranes, particularly in those making up the cristae. Treatment with digitonin is believed to disrupt the membranes along fragile lines of cleavage so that polydisperse frag-

ments result which are made up of multiples of a single structural unit, each of which may contain only a single respiratory enzyme assembly (*5, 19, 21*) (see Fig. 2). Calculations based on the known content of some respiratory carrier proteins in the liver mitochondria suggest that as much as 10 to 20 percent of the substance of the mitochondrial membrane is made up of the catalytically active proteins of the respiratory assemblies.

When the digitonin fragments are exposed to sonic vibration at 9 kcy/sec, there is a great decrease in the average sedimentation constant of the fragments without any change in the respiratory or phosphorylating activity. These findings suggest that the sonic vibration produces particles which approach in size and composition the basic recurring unit which, it has been suggested, make up the mitochondrial membrane, as is shown in Fig. 2.

The molecular and geometrical configuration of the mitochondrial membrane is a function of the oxidation-reduction state of the respiratory carriers; recent experiments have demonstrated that when the electron carriers of intact mitochondria are fully reduced the mitochondria are not susceptible to swelling in the presence of thyroxine and other agents (*22*). When the carriers are fully oxidized, the mitochondria are maximally responsive to the action of swelling agents.

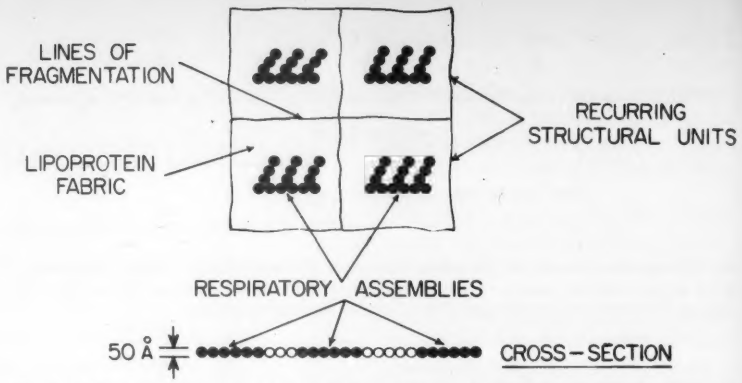

Fig. 2. Molecular representation of mitochondrial membrane. Each respiratory assembly is assumed to consist of six carrier proteins and three ancillary enzyme molecules at each coupling site to yield structure of molecular weight 1.5 million, assuming molecular weight of 100,000 for each protein. Since assembly molecules make up as much as 20 percent of the membrane, the simplest recurring unit may have a particle weight of some 7.5 million. The measured thickness of membrane suggests a monolayer of protein molecules.

Coupling Mechanism

Experimental approaches. It has been proposed by a number of investigators (see, for instance, *2, 3, 11, 23*) that at each of the three phosphorylation sites in the respiratory chain coupled electron transfer results in the formation of a "high-energy" derivative of an electron carrier, either with phosphate or with some other compound. This "high-energy" intermediate may thus be viewed as the chemical form in which the energy liberated in electron transfer has been conserved. It is then proposed that this intermediate can donate its "high-energy" phosphate group to ADP to form ATP, either directly or following intervening group-transfer reactions. Such a formulation (*2, 11*) is given in skeleton form in the following equations:

$$\text{Carrier} + X \xrightarrow{\text{electron transfer}} \text{Carrier} \sim X \quad (1)$$

$$\text{Carrier} \sim X + P_i + \text{ADP} \rightleftarrows \text{Carrier} + \text{ATP} + X \quad (2)$$

in which X is the hypothetical coupling molecule (possibly an enzyme) and $\sim$ denotes a "high-energy" bond; in all probability, X is a group-transferring enzyme.

It is evident from these reactions that two general approaches to study of the coupling mechanism are possible. The first approach, seemingly the more direct one, is to search for and identify chemically the primary "high-energy" form of the three specific respiratory carriers which engage in the energy coupling. However, although the major electron carriers in the respiratory chain are known, there is considerable uncertainty about the participation of additional carrier molecules or enzymes beyond those shown in Fig. 1. For instance, much recent activity in a number of laboratories suggests the participation of substances such as vitamin K_1, α-tocopherol, an unidentified quinone, copper (and also an additional cytochrome (c_1), but the sequence and precise role of these elements is not known, and therefore the precise location of the three phosphorylation sites is still somewhat uncertain.

On the other hand, a second approach to the coupling mechanism is implicit in the scheme of reactions 1 and 2—namely, the identification of the terminal reaction(s) leading to formation of ATP through a transphosphorylation to ADP. By working back in reaction 2 from ATP, it is evident that the mechanism of the participation of phosphate and ADP may be elucidated, in principle, before the specific electron carriers involved in coupling are identified. This is the "back-door" approach to oxidative phosphorylation, and in the following paragraphs it is shown that this approach has yielded significant new information.

The membrane fragments bring about three characteristic transformations of ATP in the absence of *net* transfer of electrons, and each of these is greatly modified by the classical uncoupling agent dinitrophenol. These are (i) adenosine triphosphatase activity (*10*), (ii) the ATP-P_i^{32} exchange reaction (*11*), and (iii) the ATP-ADP exchange reaction (*11, 24, 25*). These reactions and their significance are described in the following paragraphs.

Adenosine triphosphatase activity. The phosphorylating digitonin fragments are capable of hydrolyzing ATP to ADP and P_i (*10*). This ATP-ase activity is believed to be related to the coupling mechanism since the addition of the uncoupling agent dinitrophenol greatly accelerates the hydrolysis of ATP; in this respect the ATP-ase activity of the fragments resembles that in intact mitochondria. The ATP-ase activity is completely specific for ATP; the fragments do not act on the triphosphate of inosine, guanosine, uridine, or cytidine; this is in agreement with the complete specificity for ADP shown by oxidative phosphorylation. There is no ADP-ase activity, nor are the diphosphates of the other nucleosides attacked. The ATP-ase activity of the digitonin fragments is great enough to account for at least some of the deficit in the P:O ratios observed. Appropriate tracer experiments have revealed that the ATP-ase activity is not "turned off" during oxidative phosphorylation (*10*).

The hypothetical coupling mechanism shown in reactions 1 and 2 could account for the DNP-stimulated ATP-ase. It may be postulated that ATP is split by reversal of reaction 2 followed by hydrolytic decomposition of carrier $\sim X$; DNP is generally believed to cause rapid decomposition of an energy-rich intermediate (such as carrier $\sim X$) by a displacement reaction, leading to net hydrolysis of ATP.

Exchange Reactions

The ATP-P_i^{32} exchange reaction. When the digitonin fragments are incubated aerobically with ATP and inorganic phosphate labeled with P^{32}, in the *absence* of oxidizable substrate or net electron transport, P_i^{32} is incorporated into the terminal phosphate of ATP in a reaction which is inhibited by dinitrophenol. No other nucleoside 5′-tri- or -diphosphate will replace ATP (*11*). This exchange reaction is thus similar to that occurring in intact mitochondria, and it is believed to represent the action of a portion of the coupling mechanism (*11, 25*). The exchange reaction is inhibited by those agents which uncouple phosphorylation, but not by Ca^{++} or thyroxine. The exchange activity disappears on aging of the digitonin fragments at the same initial rate as that of the loss of activity in oxidative phosphorylation and the dinitrophenol-stimulation of ATP-ase. This property clearly indicates that a labile common factor is shared in all three reactions.

The rate of the ATP-P_i^{32} exchange reaction is modified by the presence of ADP in a manner suggesting that ATP, ADP, and P_i participate in an equilibrium (*11*). When ATP concentration is reduced to 1 m*M* or lower and the phosphate concentration is high (about 10 m*M*), then the presence of ADP becomes absolutely necessary for the incorporation of P_i in ATP. Adenosine diphosphate is thus an obligatory component of the ATP-P_i^{32} exchange reaction.

Participation of ATP, ADP, and P_i in an equilibrium could be expected by the simple hypothesis stated in reactions 1 and 2. As will be seen below, however, reaction 2 can be dissociated into two consecutive reaction steps.

The ATP-ADP exchange reaction. Direct participation of ADP in an exchange reaction with ATP was then demonstrated conclusively by incubating ADP labeled in the terminal phosphate with P^{32} together with unlabeled ATP and the membrane fragments. The ATP was then isolated by chromatography of the medium in Dowex-1 columns and was found to have become labeled (*11*). Fortunately the digitonin fragments are essentially free of adenylate kinase, an enzyme which is present in considerable amounts in intact mitochondria and which causes conversion of labeled ADP to ATP, a reaction which could "mask" and interfere seriously with the study of the ATP-ADP exchange.

On closer study, by using C^{14}-labeled ADP and paper chromatography for separation of the nucleotides, it has been found that the incorporation of ADP into ATP is in fact a very fast reaction and quickly proceeds to complete isotopic equilibrium between the ATP and ADP present (*24*).

The ATP-ADP exchange has been found to share a common denominator with the ATP-ase activity and the ATP-P_i^{32} exchange: it is inhibited (Table 1) by the uncoupling agents dinitrophenol, Dicumarol, and gramicidin in fresh preparations of digitonin fragments (*24*). It was a very important finding, the significance of which is pointed out below, that the rate of the ATP-ADP exchange reaction is not modified by the presence or the concentration of inorganic phosphate, as is seen in Table 1 (*24*).

Significance of exchange reactions of ATP. Information on these DNP-sensitive reactions of ATP obtained from the digitonin fragments is far more useful than that derived from study of intact mitochondria, in which other exchange reactions of ATP occur which are essentially extraneous to oxidative phosphorylation, such as the adenylate kinase reaction. Furthermore, intact mitochondria show morphological "compartmentation" of their "pools" of DPN, H_2O, phosphate, and nucleotides (*26, 27*), leading to great complexities in interpretation of the kinetics of these exchange reactions.

The importance of the exchange reactions of ATP in making the "back-door" approach to the mechanism of oxidative phosphorylation may now be shown. It will be seen that close study of these reactions has permitted (i) determination of the sequence and general character of the terminal reactions of oxidative phosphorylation, (ii) separation of the last enzyme in the sequence in soluble form, free of interfering reactions, and (iii) experimental approaches to the function of the respiratory carriers in energy coupling.

Sequence of interaction of phosphate and ADP. The properties and requirements of the ATP-P_i^{32} and ATP-ADP exchange reactions make it possible to establish the sequence of the terminal reactions of oxidative phosphorylation with some certainty. The over-all general equation (Eq. 2) for interaction of ADP and P_i already given, namely

$$\text{Carrier} \sim X + P_i + ADP \rightleftarrows ATP + \text{carrier} + X \quad (2)$$

can be visualized as a sequence of two consecutive reaction steps, in which the entry of phosphate and ADP occurs in separate reactions.

Here two possibilities are open, as follows:

Sequence I

$$\text{Carrier} \sim X + P_i \rightleftarrows \text{Carrier} + P \sim X \quad (3)$$

$$P \sim X + ADP \rightleftarrows X + ATP \quad (4)$$

Sequence II

$$\text{Carrier} \sim X + ADP \rightleftarrows ADP \sim X + \text{carrier} \quad (5)$$

$$ADP \sim X + P_i \rightleftarrows X + ATP \quad (6)$$

It is seen that both sequences permit P_i^{32} to be incorporated into ATP and labeled ADP into ATP, without net electron transfer. However, in sequence I, incorporation of P_i^{32} into ATP cannot occur in the absence of ADP, but incorporation of ADP into ATP would not require the presence of P_i. Sequence II demands a converse dependence of the exchange rates.

It has already been pointed out that

Table 1. Characteristics of ATP exchange reactions in digitonin fragments. The basic test system contained 0.006*M* ATP and 100 μg of enzyme N in 1.0 ml (*p*H 6.5). The test for ADP exchange contained 0.003*M* ADP-C^{14}; the test for P_i^{32} exchange contained from 0.0002 to 0.01*M* P_i^{32}. Incubation period 20 minutes, at 25°C.

Test	ATP-ADP (Δmμmole of ATP-C^{14})	ATP-P_i (Δmμmole of ATP^{32})
I. Effect of uncouplers		
None	397	68
5×10^{-5}*M* dinitrophenol	100	0
5×10^{-5}*M* Dicumarol	140	0
0.001*M* sodium azide	395	3
0.001*M* *p*-chloromercuribenzoate	0	0
II. Effect of phosphate additions		
None added	397	68
Plus 0.005*M* P_i	394	141
Plus 0.02*M* P_i	398	162
III. Effect of aging at 2°C		
Fresh	412	157
24 hours	421	74
48 hours	397	2.3
72 hours	380	0

ADP is a necessary reactant for incorporation of P_i^{32} into ATP, as required for sequence I. Furthermore, the data in Table 1 show that phosphate concentration does not affect the rate of the ATP-ADP exchange, suggesting that phosphate is not a necessary participant in the ATP-ADP exchange reaction. This was conclusively proved by demonstrating that the ATP-ADP exchange can occur at maximum rates in the absence of incorporation of labeled inorganic phosphate into ATP. The data in Table 1 show that the uncoupling agent sodium azide does not affect the incorporation of ADP into ATP but that it does inhibit the ATP-P_i^{32} exchange completely within experimental error (*24*). Furthermore, it has been found that aging of the digitonin enzyme preparation at 2°C causes complete loss of the ability to incorporate P_i^{32} into ATP, while the activity in incorporating ADP into ATP is almost completely retained (Table 1). These findings thus demonstrate clearly that phosphate and ADP are taken up in two separate reactions during the energy coupling. The data also exclude sequence II and are compatible with the formulation of sequence I as representing in principle the two terminal reactions of oxidative phosphorylation. This conclusion is also supported by recent experiments of Boyer with O^{18} as tracer (*28*); they eliminate an ADP ~ enzyme compound as an intermediate. These experiments are compatible with, but do not yet prove, the hypothesis that a covalently-bonded phosphoenzyme is the chemical form of the phosphate donor for ADP as formulated; however, current developments in the study of phosphate-transferring enzymes makes this formulation most probable.

Properties and separation of terminal phosphotransferase. The above findings indicate that the terminal reaction of oxidative phosphorylation can be designated as

$$P \sim X + ADP \rightleftarrows X + ATP \quad (4)$$

where X is an enzyme capable of undergoing reversible phosphorylation by ATP. It has been found that the enzyme can be assayed quantitatively under appropriate conditions by measuring the initial rate of the incorporation of labeled ADP into ATP. The reaction is heat-labile and has an optimum *p*H at 6.5. It is inhibited by *p*-chloromercuribenzoate, and the inhibition can be reversed by cysteine. In fresh preparations of the mitochondrial fragments, the ADP incorporation is inhibited by dinitrophenol, gramicidin, and Dicumarol, but not by azide. It is very striking, however, that when the preparations are aged at 2°C, very little of the exchange activity is lost. However, the ATP-ADP exchange gradually loses its sensitivity to inhibition by dinitrophenol on aging and ultimately becomes completely insensitive. This finding thus demonstrates that the DNP-sensitivity of the ATP-ADP exchange in fresh mitochondrial fragments is conferred on it, probably because it shares a common intermediate with a preceding reaction which is sensitive to dinitrophenol (*24*). Thus it may be postulated that neither azide nor dinitrophenol acts on the terminal reaction (Eq. 4) but on the preceding reaction tentatively designated as

$$\text{Carrier} \sim X + P_i \rightleftarrows \text{Carrier} + P \sim X \quad (5)$$

More recent experiments suggest even closer localization of the action of these uncoupling agents (*24*).

The relatively great stability of the enzyme catalyzing the terminal ATP-ADP exchange reaction is in direct contrast to the generally labile nature of the coupling mechanism and suggested the possibility that the enzyme could be separated in soluble form from the digitonin fragments. This has now been accomplished (*24*): aqueous extracts of acetone-dried mitochondrial fragments have been found to contain 90 percent of the exchange activity in soluble form. A tenfold purification of the terminal phosphotransferase activity has been effected.

The purified soluble enzyme preparation contains only traces of adenylate kinase activity, requires no dialyzable cofactors other than Mg^{++} or Mn^{++}, and has no ATP-ase activity, nor does it catalyze the ATP-P_i^{32} exchange reaction (*29*).

The importance of the separation of the terminal enzyme of oxidative phosphorylation cannot be overemphasized; having the purified enzyme at hand now makes it possible to use it as a known base to identify and reconstruct experimentally the immediately preceding reaction, and thus, by working backward, to elucidate the separate reaction steps of the coupling mechanism.

Oxidation-reduction state of electron carriers and the coupling mechanism. Study of the exchange reactions of ATP also makes possible experimental approaches to the nature of the reaction by which oxidoreduction of the respiratory carrier leads to generation of the primary high-energy compound which ultimately becomes the phosphate donor.

The formulation of reaction 1 for the participation of the carrier is noncommittal even with regard to the gross aspects of the mechanism:

$$\text{Carrier} + X \xrightarrow{\text{electron transfer}} \text{Carrier} \sim X \quad (1)$$

However, in the light of current knowledge of energy-conserving mechanisms in oxidoreductions, more specific mechanisms may be written. Actually two major reaction types are possible and have been proposed for the mechanism of oxidative phosphorylation. The first implies that the high-energy complex of a specific carrier is formed when a specific carrier is *reduced* (*3*); generation of ATP is then caused by phosphorolysis of the reduced carrier complex:

Mechanism I

$$\text{Carrier} + X + 2e \rightarrow \text{Carrier}_{red.} \sim X \quad (7)$$

$$\text{Carrier}_{red.} \sim X + P_i \rightleftarrows \text{Carrier}_{red.} + P \sim X \quad (8)$$

$$P \sim X + ADP \rightleftarrows ATP + X \quad (9)$$

On the other hand, an alternative mechanism may be written, in which the high-energy form of the carrier with X is generated by the act of oxidation or removal of electrons from a reduced carrier, analogous to the known mechanisms of energy conservation in the case of triose phosphate dehydrogenase and α-keto acid oxidases. Such a mechanism follows:

Mechanism II

$$\text{Carrier}_{red.} + X \rightarrow \text{Carrier}_{ox.} \sim X + 2e \quad (10)$$

$$\text{Carrier}_{ox.} \sim X + P_i \rightleftarrows \text{Carrier}_{ox.} + P \sim X \quad (11)$$

$$P \sim X + ADP \rightleftarrows ATP + X \quad (12)$$

These two alternative formulations thus suggest that the rate of the ATP-P_i^{32} exchange and the ATP-ase activity may be a function of the oxidation-reduction state of the respiratory carriers in the chain. If this can be shown to be true, it would constitute very important evidence for a coupling mechanism of this general type. Furthermore, such experiments could be of assistance in deciding which of the two mechanisms depicted is correct. For example, if the respiratory chain were kept in the fully reduced state, but with no net flow of electrons, the rate of the ATP-P_i^{32} exchange in mechanism I could be expected to be maximal, but in mechanism

II could be expected to approach zero. Conversely, the fully oxidized state should produce complete inhibition of the exchange in mechanism I, but a maximal rate if mechanism II is correct.

The effect of the oxidation-reduction state of the respiratory carriers on the ATP-P_i^{32} exchange as it occurs in the digitonin membrane fragments has been examined (*30, 31*). Following institution of the two extreme oxidoreduction states, which were monitored by measurement of difference spectra, it was found that the rate of the exchange reaction was maximal when the carriers were fully oxidized; when the carriers were in the reduced state, the rate of the exchange was greatly and sometimes completely inhibited. Similar results were observed in intact mitochondria when appropriate precautions were taken to measure initial rates of the exchange following full reduction of the carriers. Intermediate oxidation-reduction states yielded intermediate rates of exchange.

Because the ATP-P_i^{32} exchange reaction may proceed to isotopic equilibrium between the P_i and the terminal P of ATP rather quickly, it is evident that this exchange must occur through the intervention of a reaction intermediate *which has approximately the same energy of hydrolysis as the terminal phosphate bond of ATP.* This thermodynamic consideration makes it necessary to conclude that the *oxidized* state, which yields maximum rates of exchange, is the "energy-rich" or "charged" form of the carriers or is the primary determinant of an energy-rich intermediate ultimately responsible for the formation of ATP. This picture is thus analogous to other enzymatic oxidoreductions in which coupled synthesis of a new "high-energy" linkage occurs, as in the case of triose phosphate dehydrogenase. In both these reactions it is the *oxidative partial reaction* which is the energy-conserving phase of the over-all oxidoreduction.

These findings are not consistent with an alternative hypothesis (*3, 32*)—namely, that the *reduced* form of the carriers is the energy-rich form, which was based primarily on the finding that, in the absence of ADP, respiration of intact mitochondria ceases with the carriers largely in the reduced state (that is, combined with an inhibitor "I"). Addition of ADP caused the restoration of respiration with a shift toward the more oxidized form of the carriers in the steady state. Such properties are not dissimilar to those of the digitonin fragments, but they do not necessarily indicate the energy content of the so-called "inhibited" form of the respiratory carriers.

It is necessary to point out that there are some restrictions on conclusions drawn from experiments on the rate of the ATP-P_i^{32} exchange reaction. There are three phosphorylation sites in the respiratory chain. It is probable but not proved that all three participate in the observed ATP-P_i^{32} exchange reaction. The individual contribution of each phosphorylation site to the measured total ATP-P_i^{32} exchange rate is, however, still unknown, and it is conceivable that one of the three sites may contribute only a very small part of the observed exchange, of the order of a few percent. Obviously the dependence of this site on the oxidation-reduction state could not be determined satisfactorily by the experiments described. Furthermore, it is conceivable that the energy-rich or charged form of the carrier may be the oxidized state for only one or two sites and the reduced state for the other(s). From the statistical point of view, however, we can conclude that the oxidized state yields maximum rates of the ATP-P_i^{32} exchange and also ATP-ase activity.

With the availability of the purified terminal phosphotransferase enzyme, it is now feasible to approach in a direct manner the reconstruction of ATP-ase and ATP-P_i^{32} exchange activity. This approach is now being taken in current investigations in this laboratory and is expected to yield definite answers not only on the participation of the carriers in these reactions but on the important question of which oxidation state of the carrier is the energy-rich one.

A pattern of phosphorylating electron transport. The information obtained from study of the ATP-ADP exchange reaction and the oxidation-reduction dependence of the ATP-P_i^{32} exchange may now be formulated diagrammatically into a working hypothesis of the mechanism of phosphorylating electron transport, as shown in Figure 3, which illustrates the simplest possible form of a mechanism accounting for all the facts at hand.

The phosphorylation sites shown are those generally accepted (*2, 3*), although the evidence is as yet indirect and inferential. However, if the sites are correct in location and if no additional respiratory carriers participate in phosphorylating respiration beyond those shown, then it is interesting to note that the three coupled carrier pairs are separated from each other by single, noncoupled "connecting" carriers in a symmetrical manner. A "phosphate-collecting" enzyme could be added to this formulation to provide a common terminal reaction for formation of ATP from $X \sim P$, $Y \sim P$ and $Z \sim P$. This diagrammatic formulation is considered to be more realistic and informative than diagrams of respiratory carrier sequences without some mechanistic provision for the coupled phosphorylations which, after all, represent the whole purpose of the respiratory chain (*1, 2*). Furthermore, such a formulation demonstrates the thermodynamic necessity for having a multimembered respiratory chain, in order to quantize the liberation of respiratory energy efficiently into packets equivalent to the energy of hydrolysis of ATP.

Significance of digitonin fragments in active transport. Intact mitochondria are capable of accumulating electrolytes such as K^+, Na^+, H^+, and phosphate when oxidation and phosphorylation take place (see *33*). The digitonin fragments of the mitochondrial membrane have been found to contain a considerable amount of bound K^+, approximately 100 to 400 mμmole/mg of N. The behavior of this bound potassium has been investigated in this laboratory (*34*). It has been found that the bound K^+ is rapidly lost to the medium on aging the digitonin fragments. However the loss can be prevented if the fragments are actively oxi-

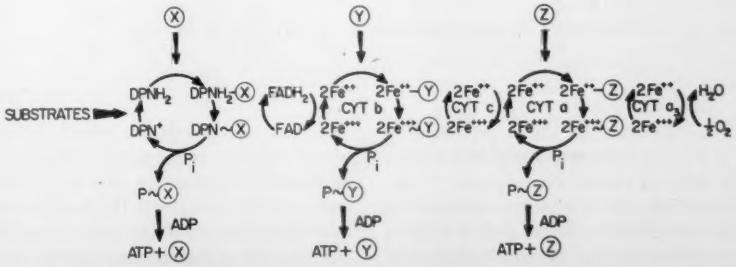

Fig. 3. Schematic representation of phosphorylating electron transport.

dizing β-hydroxybutyrate. Furthermore, active exchange of the K^+ bound to the mitochondrial membrane fragments coupled to respiration has been demonstrated with K^{42} as a tracer. It is inhibited by cyanide or dinitrophenol, demonstrating that the binding of the potassium to the digitonin fragments is linked to electron transport and phosphorylation mechanisms. However, ATP cannot substitute for respiration in causing binding of radioactive K^+. Since the preparations have relatively insignificant capacity to bind Na^+ under any conditions, this active potassium-binding mechanism of the mitochondrial membrane appears to be selective.

These experiments demonstrate that the digitonin fragments may provide an important lead for investigation of the molecular mechanisms involved in active transport; further work on identification of the binding sites for K^+ is in progress.

Conclusion

Although the membrane fragments are still highly organized, they are considerably less complex than intact mitochondria and thus relatively free of extraneous side reactions not relevant to oxidative phosphorylation and of structural "compartmentation" of pools of intermediates. With the information gained on these preparations, still less organized portions of the complex enzymatic machinery may soon be dissociated and studied separately, toward the ultimate goal of demonstrating the mechanism of oxidative phosphorylation.

These investigations are being carried out with full appreciation of the eventuality that such classical approaches to reconstruction applied to the highly integrated and structure-dependent respiratory chain and its energy-coupling mechanisms may never succeed to the same extent or in the same way as they have for other metabolic cycles which occur by interaction of essentially soluble enzymes, because of a possible necessity for special polymolecular arrangements to direct protein-protein collisions. For this reason, the problem of electron transport and oxidative phosphorylation represents a great challenge in the large and relatively uncharted area of "solid-state" enzymology.

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Retention of Radioactive Bone-Seekers

Calculations based on the power function cast doubt on the present concept of biological half-times.

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To calculate quantities pertaining to or derived from the biological retention patterns of radioactive isotopes, it is desirable to have direct measurements of retention over the entire period of interest. However, in the case of radioelements which show an affinity for bone, it is well known that the period during which retention is biologically important is usually very long and may cover the entire life span of man. The consequent paucity of data covering such extended periods of time requires that current predictions of retention and related quantities depend upon extrapolations based upon data taken over relatively short intervals.

Earlier attempts at such extrapolations were based upon the assumption that the retentions of bone-seeking radioelements decreased as first-order exponentials. Thus, a derived constant, the "biological half-life," is often used as a fundamental parameter of such retention phenomena, especially in calculations of permissible body burdens and permissible daily intakes of radioactive isotopes (*1, 2*).

Over the past several years evidence has accumulated to show that the concept of an exponential decrease in retention is altogether untenable when applied to bone-seekers. More specifically, these data show that the *over-all* retention patterns of many bone-seeking elements, when administered as soluble

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compounds readily accessible to circulating fluids, may be described in the terms of the power function. This has been well documented for the alkaline earths—calcium (*3*), strontium (*3–7*), radium (*3*; *8–11*), and, by analogy, barium—in laboratory animals. In addition, Norris *et al.* (*9*) have shown that all the available data from studies of radium metabolism in humans over a period of 25 years after administration are amenable to mathematical treatment by this method. Stehney and Lucas (*12*) used the power function to describe the increase in radium burden of human subjects at the natural level of dietary intake.

Brues and Stroud (*13*) found in mice that retention of carbon-14, given as $NaHC^{14}O_3$, followed a power function over a period of 10 months. More recently, Langham has presented data to show that the retention and excretion of plutonium-239 by man over a period of 5 years may also be described in this manner (*14*). Similarly, Bernard and Struxness (*15*) have found it applicable to the description of uranium retention by humans.

Although it is probable that the retention patterns of certain other bone-seeking elements may be described by the power function, the available data are somewhat fragmentary and usually do not extend over sufficient periods of time to be conclusive.

In this article (*16*) it is proposed, first, to appraise the value of the power function as an empirical description of the retention phenomenon, and second, to explore some of the consequences implied by its use in the mathematical treatment of retention.

General Concept of the Power Function

The members of the special class of functions having the mathematical form

$$y = x^a \qquad (1)$$

are generally referred to as power functions, and plot as straight lines on log-log paper. The applicability of this form to the description of the metabolism of bone-seeking elements is entirely empirical and of little value in the elucidation of the mechanisms involved. However, its ability to describe the retention patterns of many elements in simple mathematical fashion over extended periods of time outweighs, at least in part, the disadvantage of its empirical nature.

The mineral phase of bone undergoes several physicochemical reactions (*17*) in addition to those processes attendant upon growth and maintenance of the skeleton. As a first approach to a comprehensive mechanistic analysis, all these reactions may be considered as first-order. Recent attempts at such mechanistic analyses, by use of analog computer methods, have utilized the sum of five or more first-order exponential terms as a model (*18*, *19*).

It can be demonstrated, by graphical methods, that a sum of interrelated first-order exponential terms can often be closely approximated by a power function over a large portion of the interval of quantitative significance. For example, Way and Wigner (*20*) described the radioactive decay of mixed fission products by this method. The goodness with which a power function approximates a sum of exponentials is determined by the number of component terms and the distribution of the values of the coefficients and exponents of these terms. Where only a very few exponential terms exist, the approximation of their sum by a power function may be fortuitous, since the restrictions on the distribution of values of coefficients and exponents become severe.

In the preferred model, a sum of first-order exponentials, retention may be formally represented as

$$R_t = \sum_{i=1}^{n} \alpha_i e^{-\beta_i t} \qquad \beta_i \geq 0 \qquad (2)$$

where R_t is retention at time t following a single administration of the bone-seeking radioelement, and α_i and β_i are constants. It is tentatively hypothesized that, in normal members of a given species, the values of β_i and the number of terms, n, are independent of age. The age variable in retention is then to be found in the values of the coefficients, α_i.

However, detailed knowledge of the retention process is required before this model can be used satisfactorily as a basis for calculation and description. Therefore, experimental observations that a power function will ordinarily describe retention of bone-seeking elements are taken as the basis for the following *approximate* relationship between Eq. 2 and a form of Eq. 1:

$$R_t = \sum_{i=1}^{n} \alpha_i e^{-\beta_i t} \cong At^b \qquad -1 < b < 0 \quad (3)$$

This restriction on b is made since only over this range of values is the function of biological interest.

Mathematical Description Following a Single Dose

If q units of a soluble, bone-seeking radioactive element are administered instantaneously, the description of retention afforded by the power function is

$$R_t^* = Aqt^b e^{-\lambda t} \qquad t > 1 \qquad (4)$$

where R_t^* is retention at t units of time (days) after administration, A is a constant equal to the fraction of q retained when t is equal to 1, and b is a constant equal to the slope of the linear log-log transform of the retention function and consequently is always of *negative* sign. The quantity $e^{-\lambda t}$ is included to account for physical decay of the radionuclide, and λ is the appropriate decay constant. It is apparent that the value of $e^{-\lambda t}$ will be essentially unity when the half-life of the nuclide is much larger than the period of observation. Equation 4 may be converted to describe retention in terms of a fraction of the administered dosage by dividing by q. Hereafter R_t ($R_t = R_t^*/q$) will be expressed in these terms.

$$R_t = At^b e^{-\lambda t} \qquad t \geq 1 \qquad (5)$$

From Eq. 5, the basic equation of retention, the concomitant instantaneous *rate* of excretion is obtained by differentiating (*21*).

$$dR_t/dt = At^{b-1}e^{-\lambda t}(b - \lambda t) \qquad (6)$$

In instances where radioactive decay is not significant, λ may be assumed to have a value of zero and Eq. 6 becomes

$$dR_t/dt = bAt^{b-1} \qquad (7)$$

The quotient of Eqs. 5 and 6 gives the instantaneous coefficient of elimination (CE) which, when t is not too small, closely approximates the fraction of the retained burden being excreted per day as a function of time.

$$CE = \frac{dR_t/dt}{R_t} = \frac{b - \lambda t}{t} \qquad (8)$$

When radioactive decay may be neglected, its value varies inversely with time.

Description of Multiple or Continuous Administration

The description of retention following a single dosage may be immediately extended to describe retention resulting from multiple administrations or con-

tinuous exposure over any period of time. It is necessary, of course, to assume that the time course of retention resulting from any given dosage is not affected by previous dosages.

In the case of multiple administrations of dissimilar quantities, or of similar quantities given at long or dissimilar intervals, estimates of retained amounts (and related quantities) must be derived by summation of individual items over the appropriate time intervals. However, when repeated administrations of similar magnitude are given at reasonably short and constant intervals, the resulting retention picture can be closely approximated by assuming that the total dosage was given continuously during the total time of administration (*9*). This description of retention, $\overline{R}_t$, following continuous exposure is given by integrating the single dose retention function, Eq. 5.

$$\overline{R}_t = A \int_0^t e^{-\lambda t} t^b dt = \frac{A}{\lambda^{b+1}} \Gamma_{(\lambda t)}\,(b+1) \quad (9)$$

When λ is very small, Eq. 9 is approximated by

$$\overline{R}_t = \frac{A}{b+1}\, t^{b+1} \quad (10)$$

Equation 9 has the form of the incomplete gamma function and may be evaluated directly by reference to compiled tables (*22, 23*).

Similarly, for instances in which a period of continuous exposure to radioactive bone-seekers is terminated, if T is the time during which exposure persisted, and t is the total time of observation, the over-all retention pattern may be described as follows:

$$\overline{R}_t = A \int_0^T (t-\tau)^b\, e^{-\lambda(t-\tau)} dt \qquad t \geqq T \quad (11)$$

$$= \frac{A}{\lambda^{b+1}} \{\Gamma_{(\lambda t)}\,(b+1) - \Gamma_{[\lambda(t-T)]}\,(b+1)\} \quad (12)$$

where τ is the integration variable.

When λ is assumed to be zero in Eq. 12

$$\overline{R}_t = \frac{A}{b+1}\,[t^{b+1} - (t-T)^{b+1}] \quad (13)$$

Discussion

Because of the simplicity of its mathematical form and the ease with which its characterizing constants can be estimated, the power function offers some rather unique advantages for calculation of quantities related to the retentions of bone-seeking radioelements. Other, less empirical, methods have so far proved to be either so oversimplified as to be incapable of properly representing the available data or too complex mathematically for ready exploitation. The question whether the constants of the power function, measured in comparable individuals, are expected to vary markedly, has already been answered to some extent. Norris *et al.* (*9*), Hursh (*10*), and Floyd *et al.* (*11*) independently measured these values for radium injected into adult dogs and agreed within very narrow limits.

This approach represents a substantial improvement over presently employed concepts which somewhat ambiguously employ the term *fixed* to indicate that the rate of excretion has reached a low value. A more quantitative description is supplied by the coefficient of elimination, which is a direct measure of the lability of skeletal deposits. When far removed in time from administration, its values do not change rapidly and hence have been used to calculate quantities, erroneously called "biological half-times." It should be emphasized that the term *biological half-time* is meaningless in the context of the power function. If some similar quantity is desirable, the term *apparent biological half-time* ($T_{1/2\ \text{app.}}$) could be used with the understanding that its value is directly proportional to time after administration. Thus, from Eq. 8, for $\lambda = 0$,

$$T_{1/2\,\text{app.}} = -\frac{0.693}{\dfrac{dR_t/dt}{R_t}} = -0.693\, t/b \quad (14)$$

If it is assumed that the actual retention function follows Eq. 2, then ultimately the retention data should depart markedly from the power function description and follow a pattern determined by the exponential term of longest half-life. However, the available data in humans appear to show that this point of flexure of the retention line is not reached within 25 years in the case of radium (*9*) or within 5 years in the case of plutonium (*14*). This continuing adherence to the power function line is indicative of a failure of the bone-seeking isotope to attain a steady state in bone within the times mentioned. This may simply reflect biochemical reactions proceeding at very slow rates—rates which approach those commonly associated with solid-state diffusion. However, if diffusion (or reactions with similarly slow rates) is the rate-limiting factor for excretion of the radioelement, the bulk skeletal mineral *may* simultaneously exist in a condition of *over-all* equilibrium. This is an interesting speculation since the diffusion model, which can be thought of as comprised of a large number of closely related exponential terms, will inevitably be described by a power function. On the other hand, there may be progressive changes in the chemical or physiological status of the skeleton with time. In the latter case, an equilibrium condition would not necessarily be reached.

The above line of reasoning provides a basis for estimation of the maximum error involved in extrapolating the power function retention line beyond the point where data are available. Retention following a single dosage will be considered. The maximum possible rate of decrease in retention following the last measure of retention, R_{t_x}, is described by assuming that a steady state has been attained at t_x. Then the $T_{1/2\ \text{app.}}$ calculated at t_x may be taken as the half time of the nth, or last, exponential term, and retention henceforth will be described as

$$R_t = R_{t_x} e^{-(-b/t_x)(t-t_x)}$$

The other extreme case, the minimum possible change in retention following t_x, is represented by the assumption that retention is constant, or essentially so, following t_x. The maximum error of extrapolation now becomes

$$E_{\max.} = R_{t_x} - R_{t_x} e^{-(-b/t_x)(t-t_x)} + \hat{\sigma} \quad (15)$$

where $\hat{\sigma}$ is the error associated with the individual measurements.

Most of the work from which power function constants have been derived has been done using adult subjects. It should not be assumed that constants measured in the adult animal can be applied to the young, growing individual. The well-known fact that retention of bone-seeking elements is highest in young, growing animals guarantees some systematic changes in the power function constants as a function of rate of formation of bone.

The value of the constant A must reflect the distribution of the administered isotope in the various compartments available to it. In other words, given a fixed number of compartments, a larger value of A must indicate that relatively more of the administered element exists in compartments of longer half-life. Thus, as values of A approach unity, the corresponding values of b must approach

zero. The correlation between the values of A and b is imposed by the system of biological mechanisms that influence retention. In light of present knowledge it seems impracticable to examine this point further.

In practice, there has not been reported, in single-dose studies, an instance in which b has fallen outside the limits of 0 to -1.0. The great majority of the values have been between 0 to -0.6. Since the rate of total excretion is described by the derivative of retention, the slope of excretion curves must always be less than -1.0 and ordinarily greater than -1.6. In instances where the materials excreted in urine and feces are derived from a common source in the body, it follows that the slopes of the lines representing their rates will be identical. Langham (*14*) has shown, in the case of plutonium in man, that the values of b for urinary and fecal elimination differ. For urinary excretion the slope is greater than -1.0. This is interpreted by us as being due to slow conversion of the chemical form of plutonium in the body. Langham described this changing ratio between urinary and fecal elimination by a power function and utilized it as another method of determining time since exposure.

The power function for $b < 0$ increases without bound as t approaches zero. Therefore it cannot be used to describe retention between the time of administration ($t = 0$) and some minimum value of t—usually taken as 1 day.

It is apparent that the integrated retention function must suffer in the same fashion from this inadequate description at the earliest times. The extent to which Eq. 10 agrees with a more precise estimation of the integrated retention pattern is illustrated in Fig. 1, using constants ($A = 0.54$; $b = -0.52$) which have been found to be applicable to the metabolism of radium by adult humans. It is necessary that the log-log line representing retention following a single dose depart from its straight-line course and become asymptotic to a retention of unity at some small fraction of a day. When such a retention course is approximated, as in Fig. 1, an improved estimation of retention following continuous administration may be obtained by graphical integration. One will note that retentions following either a single or continuous administration are now described by curves which, on log-log paper, resemble hyperbolas with the asymptotes being the total administered quantity and the power function line. Thus, Eq. 10 will somewhat overestimate retention following continuous administration (although never by more than the quantity administered during 1 day) by an amount which varies with time of observation and the value of b.

With slight modifications the power function can be made to conform to the physical requirement that retention must be unity when $t = 0$. The modified form (*24*) representing retention following a single dose is

$$R_t = \frac{(t+\gamma)^b e^{-\lambda t}}{\gamma^b}$$
$$t \geqq 0; -1 < b < 0; 0 < \gamma \quad (16)$$

where γ is a constant. This form approaches Eq. 5 asymptotically as t increases and satisfies the requirements discussed in the preceding paragraph. It can readily be integrated and differentiated and offers advantages in description, especially over time intervals close to administration.

The estimation of γ requires data for sufficiently large t to determine accu-

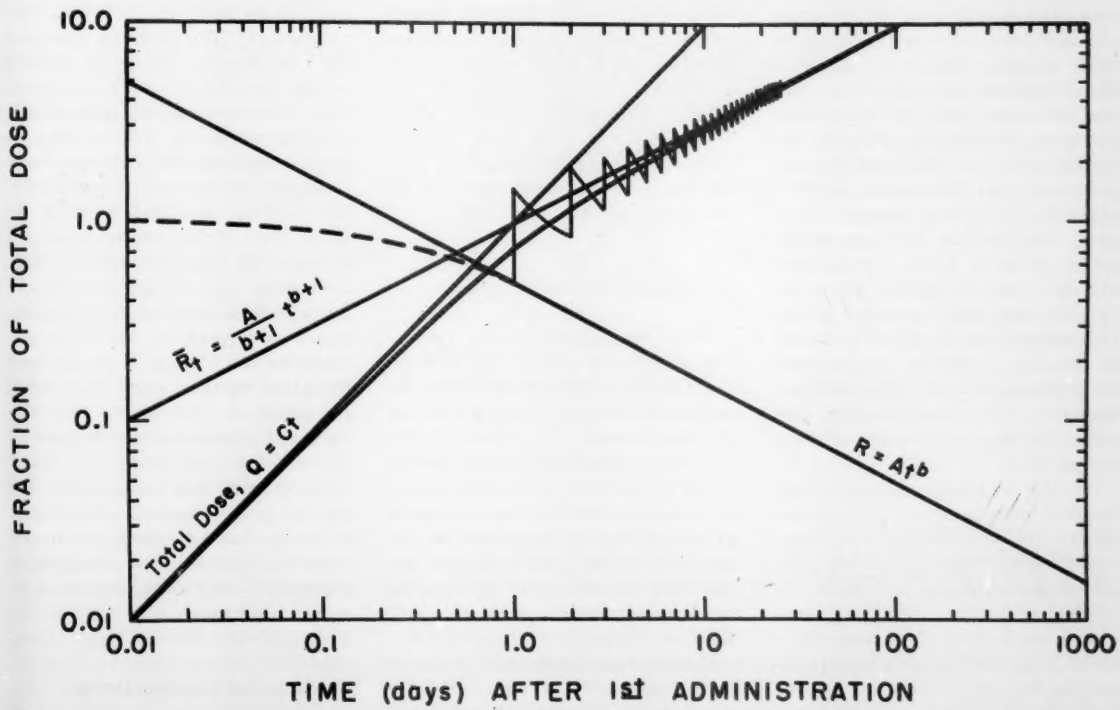

Fig. 1. Illustration of the degree of applicability of the power function at early times after administration. The curved lines are required by physical considerations for a more accurate description at early times. These may be obtained by use of Eq. 16. The saw-tooth curve illustrates the similarity of retention between repeated doses of 1 unit per day $\left[R_t^* = A \sum_{i=1}^{n} q_i (t - t_i)^b\right]$ and continuous administration of the same amount.

Table 1. Calculated values of permissible quantities absorbed daily into the blood and associated skeletal radiation dosages for selected bone-seeking radioelements in humans.

Item	Radium-226	Strontium-89	Strontium-90–Yttrium-90	Calcium-45
Mean energy (electron volt/disintegration)*	10.8×10^6†	0.511×10^6	0.987×10^6	0.089×10^6
Rads per microcurie day‡	0.079	0.00374	0.00722	0.00065
Present permissible body burden for occupational exposure (μc)§	0.1	2.0	1.0	14.0
Power function constants				
A	0.54‖	0.95#	0.95#	1.0#
b	−0.52‖	−0.254#	−0.254#	−0.134#
Intake period: 70 years**				
Daily dose to reach permissible level (μc/day)	6.8×10^{-4}	0.066	7.53×10^{-4}	0.119
Internal dose				
Microcurie days	1723	51,000††	18,140‡‡	357,700‡‡
Rads	136	190	131	232
Intake period: 30 years**				
Daily dose to reach permissible level (μc/day)	1.02×10^{-3}	0.066	1.02×10^{-3}	0.119
Internal dose				
Microcurie days	738	21,900††	6964‡‡	153,300‡‡
Rads	58.3	80	50.3	99.6
Time to equilibrate body burden				
Days to 96% of asymptotic value		209	3.9×10^4	653
Days to 100% of asymptotic value		1239	2.318×10^5	3570

* Values for β-emitters are taken as 0.35 E_{max}. † Assuming 30 percent retention of radon and its daughters. ‡ Assuming uniform distribution in a skeletal mass of 7000 g. § Values taken from the recommendations of the International Committee on Radiological Protection (*31*). ‖ Norris (*9*). # Marinelli (*32*) ** Calculations based on data for adults (see text). †† Microcurie days for Sr^{89} and Ca^{45} assume a constant burden for the entire period. ‡‡ Integrated radiation dosage determined graphically.

rately *b*. If recording times of the retention values are assumed to be error-free and if the number of measurements at each time point is equal, the weighted least squares procedure on the log transforms of the variables will yield efficient estimates of both the constants and their associated errors. The appropriate weighting factor (*24*) for each transformed retention value is the retention value itself corrected for radioactive decay. By using this method it can be shown that γ is most readily evaluated from the relationship $A = 1/\gamma^b$, where *A* is the 1-day intercept of the power function line. When a suitable portion of the *t* values are not large enough to define suitably the power function asymptote, estimates of the constants may sometimes be determined by using Eq. 16 directly and employing the general method for fitting nonlinear equations (*25*). The estimation procedure, in this case, requires extensive computation.

All the arguments and the power function constants presented herein are derived from studies in which the bone-seeking isotopes were immediately available to the circulating body fluids—for example, by intravenous injection. When such is not the case, it is necessary to introduce appropriate correction factors, such as, for example, intestinal absorption which, as a rule, is not quantitative. Marinelli *et al.* (*26*) have demonstrated that radium sulfate that is inhaled into the human lung does not go readily into solution. This situation was analyzed, by the power function method, as essentially an instance of continuous systemic administration due to the continuing solubilization of the material.

The power function may also be applied to the analysis of the situation in which a bone-seeking element is formed within the body as a result of radioactive decay of a parent element. Thus Gustafson *et al.* (*27*) concluded that the Ra^{223} arising from deposited Th^{227} behaved as if it were being continuously administered intravenously, a finding that is in agreement with data reported by Van Dilla *et al.* (*28*).

Calculation of Permissible Levels

These formulations permit calculation, with greater accuracy than is otherwise possible, of the allowable daily absorption of radioactive bone-seekers into the blood stream (*29*). Given a value for the permissible body burden and the period of exposure, Eq. 9 can be used to determine the amount of isotope which, if absorbed daily, can be expected to produce this burden by the end of the exposure period. This method has been discussed in detail by Healy (*30*).

Values for permissible daily intakes of Ra^{226}, Sr^{89}, Sr^{90}-Y^{90}, and Ca^{45} have been calculated from Eqs. 9 and 10 and are presented in Table 1. [The final body burden is that proposed in 1955 for industrially exposed persons by the International Commission on Radiological Protection (*31*)]. The power function constants for strontium and calcium in humans are based on results of a survey of the literature by Marinelli (*32*) and were obtained from studies following intravenous administration to adults. The constants for Ra^{226} are taken from Norris *et al.* (*9*). The results are presented for two somewhat arbitrarily selected periods of intake, 30 years and 70 years, which may be representative, respectively, of a working lifetime under industrial conditions and a life span under conditions of universal contamination. No effort has been made to break the figures down further into concentrations in air, water, and food, since the basic assumption requires only that the elements be freely accessible to body fluids, regardless of mode of intake. No consideration has been given to the more specialized situation which exists during the period of rapid skeletal growth in childhood and adolescence. Values calculated for the adult should be examined critically before they are applied to this segment of the population. The 70-year values in Table 1, which include the period of childhood, were calculated on the basis of adult values and are incorrect to this extent.

Calculation of Radiation Dosage

The power function may also be used to calculate integrated radiation dosage from deposits of radioactive elements in bone. The mathematical considerations

are essentially identical with those discussed with reference to retention. Since radiation dosage accumulates as the product of concentration of the radioelement and time, the integrated dosage over t days, D_t, is

$$D_t = kf(R) \qquad (17)$$

where k is the radiation dosage rate per day per microcurie in the skeleton (*33*). The quantity $f(R)$ is in every case the appropriate retention function integrated with respect to t over the period in question. It seems most reasonable to integrate over the entire period from zero time, since the inadequacies of the power function during the first day will not introduce appreciable error unless the total period of observation becomes quite short. In such a case, one should use Eq. 16 or, alternatively, integrate from 1 to t and add the best graphically determined estimate for the contribution from 0 to 1 day. From Eqs. 5 and 10 the appropriate values for $f(R)$ are, for single administration ($\lambda > 0$):

$$f(R) = \int_0^t Ae^{-\lambda t} t^b dt = \frac{A}{\lambda^{b+1}} \Gamma_{(\lambda t)}\,(b+1) \qquad (18)$$

for a single administration ($\lambda = 0$):

$$f(R) = \int_0^t At^b dt = \frac{A}{b+1}\, t^{b+1} \qquad (19)$$

for continuous administration ($\lambda \doteq 0$):

$$f(R) = \int_0^t \frac{A}{b+1}\, t^{b+1} dt = \frac{A}{(b+1)(b+2)}\, t^{b+2} \qquad (20)$$

The $f(R)$ for continuous administration with $\lambda > 0$, Eq. 9, is not readily integrated and should be determined graphically.

Values for integrated radiation dosages from permissible quantities of Ra^{226}, Sr^{89}, Sr^{90}-Y^{90}, and C^{45} accumulated by continuous exposure have been calculated and included in Table 1.

In such calculations there is the major complication that bone-seeking elements, when administered over short periods of time relative to the life span, are rarely, if ever, found uniformly distributed in the skeleton. At this time there is no accurate basis for estimating the actual spectrum of concentrations, and somewhat arbitrarily selected values must be included to compensate for this heterogeneity. However, in instances where intake of radioactive elements at a more or less constant rate has persisted for long periods up to the entire lifetime of the individual, it is to be expected that the skeleton will be uniformly radioactive (*34*), hence uniformly irradiated. Here the method of calculation gives accurate values.

It has been assumed that the radiations are completely absorbed by bone tissue. Since this may not always be the case, correction may sometimes be necessary to compensate for this loss. However, considerations of this nature are outside the scope of this discussion.

From the aspect of total radiation dosage, with respect to situations in which the permissible body burden will be found following some period of time, t, there may exist considerable differences, depending upon the mode of accumulation. This is best illustrated by comparing the two extreme cases: (i) a single administration of the bone-seeking element in such quantity that the tolerable body burden will obtain at time t, and (ii) continuous administration at such a rate that the same body burden will occur at the same time t. Since the final burdens are to be identical, Eqs. 4 and 10 with $\lambda \doteq 0$ provide the following relationship:

$$qAt^b = \frac{CA}{b+1}\, t^{b+1}$$

$$q/C = t/(b+1) \qquad (21)$$

where C is the daily dosage, between the quantities given singly and on a continuous daily basis, to bring about this condition. The relationship between the accumulated radiation dosages ($\lambda \doteq 0$) becomes:

$$\frac{D_t}{\bar{D}_t} = \frac{\frac{Aq}{b+1}\, t^{b+1}}{\frac{AC}{(b+1)(b+2)}\, t^{b+2}} = q(b+2)/Ct \qquad (22)$$

or, substituting from Eq. 21 to impose the condition of equal final burden:

$$D_t/\bar{D}_t = (b+2)/(b+1) \qquad (23)$$

Thus, in the case of radium where $b = -0.52$, there is a safety factor of 3 in total integrated radiation dosage when the body burden is achieved by daily increments. This is a minimum figure since this manner of exposure necessarily results in a more uniform concentration (that is, smaller local concentration factors) than would be found following a single injection. Since concentration factors of at least 10 have been demonstrated for radium in the bone of humans who have received radium over short periods of time, it follows that total radiation dosage to parts of the skeleton may vary by at least a factor of 30, depending upon the mode of administration, with the same final body burden in either case.

Therefore, neither "permissible body burdens" nor resulting radiation damage can be considered to be independent of method of exposure. The large factors in integrated radiation dosage which appear when single dose and continuous exposure are compared again point to the inadequacies of current procedures for assessing the hazards of bone-seeking radioelements.

Conclusion and Summary

The power function has been found to provide a satisfactory empirical description of the retention of several radioactive isotopes which are preferentially deposited in skeletal tissue. The extent to which it may apply to bone-seeking elements in general is not yet known.

The ease of mathematical manipulation of the power retention function allows the derivation of several relationships which can be used to determine permissible daily intake or integrated radiation dosage, or to evaluate important factors relating to individuals who have already accumulated skeletal deposits.

The power function indicates clearly that, in its area of application, the concept of "biological half-times" is completely fallacious and may result in gross errors both actually and conceptually.

The method offers opportunities for more accurate and realistic approaches to the problems of poisoning by radioelements as well as in calculations of allowable daily intake levels and body concentrations of radioactive bone-seekers. It indicates that major differences in integrated radiation dosage may obtain, depending upon the conditions of exposure, and points out that "permissible body burdens" should be assessed in view of the manner in which the body burden is obtained.

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$$k = \frac{3.7 \times 10^4 \times 8.64 \times 10^4 \times 10.8 \times 10^6}{7 \times 10^3 \times 6.24 \times 10^{11} \times 10^2} = 0.079 \text{ rad}/\mu\text{c day}.$$
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News of Science

Awards and Prizes at AAAS Meetings

To meet requests for information, an outline of the essential facts of the seven awards administered by the AAAS, and announced or presented at the annual meetings of the Association, is given here.

The Newcomb Cleveland Prize. This oldest award of the Association, originally known as the "AAAS Thousand Dollar Prize," has been administered since 1923. The donor, the late Newcomb Cleveland of New York, a life member of the Association, preferred to remain anonymous until his death in 1951. His bequest ensures the continuation of the prize, now given his name by the AAAS Board of Directors.

The Newcomb Cleveland Prize is unique in that it is given to the author(s) of a noteworthy paper, representing an outstanding contribution to science, presented in a regular session, sectional or societal, during the AAAS annual meeting. The Prize Committee, necessarily rather large, is composed of board members and others appointed by the president; their decision is reached at the end of the last day. It was always Cleveland's wish that this prize should be awarded each year to one of the younger scientists. Among the winners to date, each has received additional recognition and three have become Nobel Prize winners, in the later years indicated: Hermann J. Muller (1927) 1946; Wendell M. Stanley (1936) 1946; and I. I. Rabi (1939) 1944. The Newcomb Cleveland Prize will be awarded for the thirty-first time at this year's Washington meeting.

It is not necessary that the prize winner be a member of the Association. To be eligible a paper should consist primarily of the presentation for the first time of the results of the author's own research. Presidential and vice-presidential addresses, review papers, and comparable material that deals with either the research of others or with a review of the author's own previously published research accomplishments are not eligible. The prize committee will be listed in the 1958 General Program-Directory, available in early December.

Theobald Smith Award in Medical Sciences. The Theobald Smith Award in Medical Sciences of the AAAS was established in 1936 by Eli Lilly and Company, and will be given for the fourteenth time at this year's meeting. Again, without exception, the previous winners have received additional recognition subsequently.

The award, which consists of $1000 and a bronze medal, is given for "demonstrated research in the field of the medical sciences, taking into consideration independence of thought and originality." Travel expenses incurred in attending the AAAS meeting and receiving the medal are paid in addition. The recipient must be less than 35 years of age on 1 January of the year in which the award is to be made, and a citizen of the United States. Candidates do *not* apply for consideration but are nominated by AAAS fellows. The award is announced at the Association's annual

meetings during a session of Section N–Medical Sciences.

The Theobald Smith Award Committee, appointed by the president of the Association, consists of four fellows of Section N and the chairman and secretary of that section, ex officio. The names of this year's judges were reported in the 1 August issue of *Science* [**128**, 242 (1958)].

AAAS Socio-Psychological Prize. The AAAS Socio-Psychological Prize, first awarded in 1952, has been made possible by an anonymous donor. This prize is offered to encourage studies and analyses of social behavior based on explicitly stated assumptions or postulates, which lead to testable conclusions or deductions. In short, the prize is intended to encourage in social inquiry the development and application of dependable methodology analogous to the methods which have proved so fruitful in the natural sciences.

Hitherto unpublished manuscripts are eligible, as are manuscripts which have been published in the award year. Entries may be of any length, but each should present a completed analysis of a problem, the relevant data, and an interpretation of the data in terms of the postulates with which the study was begun. Entries may be submitted by the author himself or by another person on his behalf. Details of the conditions were given in the 21 March issue of *Science* [**127**, 636 (1958)].

Entries are judged by a committee of three persons selected each year by a management committee consisting of the chairman and secretary of Section K–Social and Economic Sciences and the executive officer of the AAAS. The judges reserve the right to withhold the prize if no worthy essay is submitted. The judges for this year are Harry Alpert, National Science Foundation; Melville J. Herskovits, Northwestern University; and Donald G. Marquis, Social Science Research Council.

AAAS-Anne Frankel Rosenthal Memorial Award for Cancer Research. In 1955, the Association began to award annually the AAAS-Anne Frankel Rosenthal Memorial Award for Cancer Research. The award, supported by the Richard and Hinda Rosenthal Foundation, consists of $1000 and is given for outstanding research by a scientist resident in the United States. In proposing the award, the foundation stated: "We do not wish to exclude an outstanding advance on the more applied, or even clinical, level, but we do wish to make it quite clear that very basic pieces of research would surely qualify for primary consideration."

Members of the award committee are Warren Weaver, Rockefeller Foundation, *chairman*; Harry S. N. Greene (American Association for Cancer Research), Yale University School of Medicine; G. Burroughs Mider, National Cancer Institute; Richard L. Rosenthal, Richard and Hinda Rosenthal Foundation; C. Chester Stock, Sloan-Kettering Institute for Cancer Research; and Harry M. Weaver, American Cancer Society. Each year this committee nominates a recipient prior to the Association's annual meeting during the last week in December. The nomination, after approval by the Board of Directors of the Association, is announced at the annual meeting. The fourth award will be announced in December 1958.

The committee, using suggestions received from its own membership and from whatever proposals it may see fit to solicit, considers only work that has been reasonably fully reported to the scientific community through the usual oral or printed channels, so that the work has been subject to the usual processes of general scientific judgment regarding its validity and importance.

AAAS-Ida B. Gould Memorial Award for Research on Cardiovascular Problems. Beginning in 1956, an annual award of $1000 for research on cardiovascular problems, also supported by the Richard and Hinda Rosenthal Foundation, is administered by the AAAS. The methods of selection of the recipient and the criteria for making this award are quite similar to those for the AAAS-Anne Frankel Rosenthal Memorial Award for Cancer Research. Members of the award committee are: Paul Dudley White, Boston, Massachusetts, *chairman*; C. Sidney Burwell (Helen Hay Whitney Foundation), Harvard Medical School; Robert P. Glover (American College of Cardiology), Presbyterian Hospital, Philadelphia; Dickinson W. Richards (Life Insurance Medical Research Fund), Bellevue Hospital, New York; Richard L. Rosenthal, Richard and Hinda Rosenthal Foundation; Francis C. Wood (American Heart Association), University of Pennsylvania Hospital; and J. Franklin Yeager, National Heart Institute.

AAAS-Campbell Award for Vegetable Research. The AAAS-Campbell Award for Vegetable Research, supported by the Campbell Soup Company, was given for the first time last year during a session of Section O–Agriculture.

The award consists of $1500 and a bronze medal, given for "an outstanding single research contribution, of either fundamental or practical significance, relative to the production of vegetables, including mushrooms, for processing purposes, in the fields of horticulture, genetics, soil science, plant physiology, entomology, plant pathology, or other appropriate scientific areas." Work in food technology and food processing are *not* included; the emphasis is on basic research and applications thereof variously concerned with crop production, prior to crop utilization or crop processing.

The one or more papers reporting this single research should have been published—or the manuscripts must have been accepted for publication—in a recognized scientific journal, not more than 2 years prior to the date of granting the award, which is open to all residents of the United States and Canada. Travel expenses for the recipient, to attend the AAAS meetings and to receive the award in person, are paid in addition.

The Award Committee is composed of a chairman appointed by the AAAS and official representatives of six affiliated societies. Members of the Award Committee are Louis P. Reitz (past chairman and committeeman-at-large, Section O), U.S. Agricultural Research Service, Beltsville, Maryland, *chairman*; G. J. Haessler (Entomological Society of America), U.S. Agricultural Research Service, Beltsville, Maryland; Sterling B. Hendricks (American Society of Plant Physiologists), U.S. Plant Industry Station, Beltsville, Maryland; Iver J. Johnson (American Society of Agronomy), Iowa State College; F. C. Stark, Jr. (American Society for Horticultural Science), University of Maryland; G. Ledyard Stebbins, Jr., (Genetics Society of America), University of California, Davis; and E. E. Wilson (American Phytopathological Society), University of California, Davis.

Section P Industrial Science Award. At the Association's New York meeting of 1956, Section P–Industrial Science inaugurated an annual award for an outstanding achievement in technology by an American industrial firm. The first citation, on a scroll, was presented to the General Electric Company, at a dinner, for a fine-particle iron magnet developed by their instrument department at Lynn, Mass. The second citation, last year, was made to P. R. Mallory & Company for their development of the Steelmet process in powder metallurgy. The current officers of Section P are Frank C. Croxton, Battelle Memorial Institute, chairman; and Allen T. Bonnell, Drexel Institute of Technology, secretary.

RESA's William Procter Prize. If the William Procter Prize, given annually by the Scientific Research Society of America to an eminent engineer or scientist, is included, a total of eight awards or prizes are now announced or presented at the annual meetings of the Association. The RESA award is associated with the series of annual addresses with the Association sponsored by the society. The distinguished speaker is the recipient the society's judges have chosen.

Complete lists of the recipients of all

AAAS-administered awards and the current committees of judges will be found in each year's General Program-Directory which becomes available to advance registrants and others early in December. (Coupons for ordering the directory will be found in the advertising pages of *Science* at frequent intervals.)

RAYMOND L. TAYLOR

AAAS

Program for the International Conference on Scientific Information

The program for the International Conference on Scientific Information, which is scheduled to be held in Washington, D.C., at the Mayflower Hotel 16–21 November 1958, is in its final stages of development. On the evening of 16 November, the conference will be officially opened by an address by Sir Lindor Brown, secretary for Biological Sciences, the Royal Society. On the evening of 19 November, there will be a banquet at which Detlev W. Bronk, president, National Academy of Sciences, will be the chief speaker.

A total of 75 papers prepared by 98 authors and coauthors has been accepted and printed for distribution in advance of the conference to all participants (authors and members of discussion panels) and registered observers. These papers will serve as a basis for panel discussions, arranged according to the seven areas of the program agenda and chaired by the following persons:

Area 1. Requirements of scientists for scientific literature and reference services: knowledge now available and methods of ascertaining their requirements. (Panel leader: Philip Morse, department of physics, Massachusetts Institute of Technology.)

Area 2. The function and effectiveness of abstracting and indexing services for storage and retrieval of scientific information. (Panel leader: Elmer Hutchisson, American Institute of Physics.)

Area 3. Effectiveness of scientific monographs, compendia, and specialized information centers in meeting the needs of scientists: present trends and new and proposed techniques and types of services. (Panel leader: Alexander King, European Productivity Agency.)

Area 4. Organization of information for storage and search: comparative characteristics of existing systems. (Panel leader: Eric de Grolier, Centre Français d'Echanges et de Documentation Techniques.)

Area 5. Organization of knowledge for storage and retrospective search: intellectual problems and equipment consideration in the design of new systems. (Panel leader: Gilbert W. King, I.B.M. Research Center.)

Area 6. Organization of knowledge for storage and retrospective search: possibility for a general theory of storage and search. (Panel leader: John W. Tukey, department of mathematics, Princeton University.)

Area 7. Responsibilities of governmental bodies, professional societies, universities, and research and industrial organizations to provide improved information services and to promote research in documentation. (Panel leader: Verner Clapp, Council on Library Resources.)

Also in attendance will be approximately 500 observers from some 20 foreign countries who already have registered to attend as observers.

In addition to the program discussion sessions, several excursions are planned to such installations as the National Bureau of Standards, the Library of Congress, and other agencies engaged in activities relevant to the conference program.

The conference will close with a reception for participants at the National Academy of Sciences on Friday evening, 21 November 1958.

U.N. Radiation Committee as a Permanent Body

Dag Hammarskjold, Secretary General of the United Nations, has proposed that the United Nations Scientific Committee on the Effects of Atomic Radiation be established as a permanent U.N. body and its functions expanded. After consultation with member scientists of the 15-nation committee, most of whom expressed enthusiasm for continuing their work, Hammarskjold made his recommendation in a report that has been distributed to the General Assembly. The report included the suggestions that, as a permanent group, the committee might (i) serve as an international clearinghouse for radiation information, (ii) establish an international monitoring system for the detection of radioactivity, both natural and man-made, (iii) sponsor conferences and seminars, and (iv) regularly publish a bulletin for distribution to scientists.

Type Culture Collection

The American Type Culture Collection has announced that the sixth edition of its catalog of cultures will be available for distribution soon after 1 September. It lists 4350 strains of microorganisms, including bacteria, bacteriophages, filamentous fungi and yeasts, algae and protozoa. A special section lists organisms having particular applications, as in microbiological assays, production of antibiotics and vitamins, and biochemical transformations.

Previous editions of this catalog have been subsidized by the Society of American Bacteriologists and have been distributed without charge. Upon the recommendation of the several national biological societies, sponsors of the ATCC, a policy has now been adopted of making a nominal charge of $1 (postpaid) for the catalog to offset the cost of printing and mailing and to provide funds against which the expense of preparing future revisions can be charged without waiting for a special subsidy for the purpose. It is expected that this will result in keeping the catalog revisions more nearly current with the growth of the Collection. The present revision is the first since 1949.

Orders for the catalog should be sent to the American Type Culture Collection, 2112 M St., NW, Washington 7, D.C.

Revisions of the ATCC catalogs of viruses (human, animal, and plant) are also in progress and are expected to be completed this year. The Viral and Rickettsial Registry, which was established in 1950, is henceforth to be known as the ATCC Viral and Rickettsial Registry and Distribution Center. It has received a grant of $1000 from the Rockefeller Foundation, and is assured of one for $5000 from the National Institutes of Health (to improve and expand its services in the acquisition, preservation, and distribution of prototype strains of viruses and rickettsiae, thus keeping pace with the increasing research interest in these agents. A committee of six virus specialists, including F. B. Gordon, R. J. Huebner, J. L. Melnick, Morris Schaeffer, R. L. Thompson, and Joel Warren has been set up as the policy formulating group for this activity.

Geological Survey Field Work

Field work is being carried on this year in the Geologic Division of the United States Geological Survey by nearly 200 field parties. Many field projects include the preparation of geologic maps. Other studies entail measurements of magnetic, electrical, and other properties of the earth by geophysicists in areas as diverse as a floating ice island in the Arctic Ocean and a desert basin in Nevada. Still other field work involves geochemists and geobotanists whose field measurements and collections of specimens provide data on the distribution of the small amounts of metals in plants and rocks to guide those seeking commercial concentrations of these metals.

This year many new projects are starting: in general, they are aimed at

evaluating the mineral resource potential of an area, or gaining geologic knowledge to aid land development for engineering use. The following partial list of the Survey's new field projects serves to give some idea of the scope and purposes of current field investigations: Mississippi Embayment, western Tennessee—a study of water-bearing formations that are important sources of ground water; Barter Island and Mount Chamberlain areas, Alaska—a study of the effects of Arctic conditions on engineering construction, and of understanding the geology of the Arctic; barite resources of west-central Arkansas; porphyry copper deposits of the western United States; Salinas Valley, Calif.—a study of the oil and gas potential; coal resources of Washington; Sierra Nevada batholith, California—a study of the granite rocks and associated mineral deposits of this great mountain range; T-3 Ice Island, Arctic Ocean—electrical and seismic studies that are expected to provide new information on the nature and configuration of the material beneath the Arctic Ocean.

Nuclear Explosions and Isotopes from Power

The Atomic Energy Commission is undertaking studies to determine the practicability of producing both power and radioisotopes from nuclear explosions. As a first step in the studies, consideration is being given to the detonation of a small device underground in the salt-bed area known as the Solado formation in the Delaware Basin, Eddy County, New Mexico, about 25 miles southeast of Carlsbad.

The project, if carried out, would be conducted in the summer of 1959 in a 1200-foot shaft drilled into the salt beds so that heat developed by the nuclear explosion would be confined to a relatively small area. Neutrons created in the nuclear reaction would be used to produce radioisotopes. General scientific information on scaling laws, seismic effects, and geological data also would be obtained. As now planned, the yield of the explosion would be about 10 kilotons, the equivalent of 10,000 tons of high explosive.

The technical work is being conducted by the University of California Radiation Laboratory, Livermore, and the planning is under the supervision of the commission's San Francisco Operations Office. The project manager for the demonstration is James E. Reeves of the commission's Albuquerque Operations Office, and the technical director is Gerald W. Johnson, Test Division Leader, UCRL, Livermore.

The New Mexico experiment is the second initiated under the commission's Plowshare Program to investigate important peacetime applications of nuclear explosives. As previously announced, studies are being conducted on the Alaska Coast between Cape Seppings and Point Hope to determine the practicability of excavating a harbor.

Century 21 Exposition

A world fair, emphasizing science and its relationship to the development of man, will receive the help of a group of leaders in American science.

Seventeen scientists from the academic world, industry, scientific associations, and scientific journals will go to Seattle, Washington, this month to work with exposition officials in the development of plans.

The fair, which has been in the initial planning stage since 1955, is scheduled to open in May 1961 on a 70-acre site in Seattle.

The science theme of the exposition was decided upon when officials connected with the project found that science leaders were seeking a means of putting on a fair in 1961 to give a dramatic presentation of the results of the International Geophysical Year. In addition to the IGY theme, the exposition will ask and attempt to answer the question "Where is science going during the next 100 years?"

Although the basic theme will be science, the fair, which will be called Century 21 Exposition, will also mark the centennial of the University of Washington and the admission of Alaska as a state. The commercial relationship of the city of Seattle with the nations rimming the Pacific Ocean will also be stressed by exhibitions in a Pan-Pacific section. The fair is expected to be international in character, with the Soviet Union, Italy, Japan, and other nations participating. A bill currently before the United States Congress would make the Federal Government a participator.

Maps for Disease Control

Among the scientific publications to appear in West Germany since the war is a series of atlases which trace graphically the movement of epidemic and endemic diseases throughout the world. Two volumes of this work have been published since 1945, and part 2 of volume 3 will appear shortly. Whereas volumes 1 and 2 are confined principally to Europe, North and South America, and Africa, volume 3 covers Asian countries. These atlases contain medical and scientific information on the spread and control of epidemic and endemic diseases; facts about geography, history, and climate; and population surveys.

The correlation and graphic presentation of all the factors involved in the control of contagious disease is the lifework of a group of scientists and professors in the Geomedical Research Station of the Heidelberg Academy of Sciences. The studies were begun before World War I; after 1945 the U.S. Navy interested itself in the continuation and extension of the work and volume 1 of the present series was published under Navy auspices in 1952. Volumes 2 and 3 have been published by the Heidelberg Academy and the Falk Publishing House of Hamburg.

News Briefs

A special committee of the International Geophysical Year has voted for a 1-year extension of the 18-month IGY program, originally set up to end in December 1958. The extension period would be known as the "International Geophysical Cooperation of 1959." Although the committee agreed to extend the research, it still will be necessary to get the 60 participating governments to provide financial support.

* * *

Wallops Island, Virginia, will become the Cape Canaveral of the government's new National Aeronautics and Space Administration if present plans are approved. A $24.5-million expansion of facilities at the island has been proposed by the National Advisory Committee for Aeronautics. The island is a 3200-acre strip off the Eastern Shore where NACA has been testing rockets for 13 years.

* * *

The first Electronic Computer Exhibition ever held in the United Kingdom will be staged in London from 28 November to 4 December. More than 40 British manufacturers are exhibiting. A symposium on the applications of computers to problems in business, industry, and science will be held with the exhibition. Also, immediately before the exhibition, 24–26 November, an associated scientific symposium on "The Mechanization of Thought Processes," organized by the National Physical Laboratory, will be held at Teddington, Middlesex, England.

* * *

The University of Chicago has established a Graduate School of Education. Francis S. Chase, chairman of the department of education, has been appointed dean of the school. Creation of the graduate school does not replace or eliminate the existing department of education, which continues its present activities, particularly those of research and instruction for graduate students in

general areas of education. The new school will administer programs of teacher preparation leading to the Master of Arts in Teaching degree and also will be the administrative unit for a variety of interests of the department.

* * *

The Atomic Energy Commission has established an Office of Hearing Examiner to conduct assigned hearings. The new office has been set up to fill the commission's requirement for hearings and to keep pace with the growth of the regulatory functions of the commission. The office will be directly responsible to the commissioners. Samuel W. Jensch has been appointed hearing examiner.

* * *

Abstracts of the 319 papers presented at the International Congress of Radiation Research held in Burlington, Vt., 10–16 August, are included in the July 1958 issue of *Radiation Research*, which is the official organ of the Radiation Research Society, published by Academic Press Inc., New York.

* * *

Some 70 nuclear scientists and engineers from nearly 25 countries who are graduates of the International School of Nuclear Science and Engineering at the Argonne National Laboratory will hold an alumni reunion at Geneva, Switzerland, on 6 September during the second United Nations International Conference on the Peaceful Uses of Atomic Energy. This is probably the first alumni reunion of any school or any training program which is totally international in character. Basic support for the alumni day has been provided by the University of Chicago, which operates Argonne under contract with the Atomic Energy Commission.

Grants, Fellowships and Awards

Conservation. The National Wildlife Federation and its state affiliates offer a number of scholarships and fellowships for work in conservation or conservation education. Activities that might be considered appropriate include: teacher training, radio and television, scouting and conservation, curricular problems, farmer-sportsmen relationships, conservation workshop techniques, textbook development, journalism, and state programs. An applicant need not necessarily be enrolled at an institution of higher learning if his project has merit in the cause of conservation. Application blanks, which must be submitted by *1 November,* may be obtained from: Executive Director National Wildlife Federation, 232 Carroll Street, N.W., Washington 12, D.C.

General. The American Association of University Women has announced 40 fellowships open to women in 1959–60. They are offered (i) to women who already hold the doctorate and (ii) to women who have completed all requirements for the doctorate except the dissertation. These fellowships are unrestricted as to field and place of study, except that one is specified as postdoctoral in the field of physics, chemistry, or biology. The stipends range from $2000 to $4000. Application forms may be obtained from the Director, AAUW Fellowship Program, 1634 I St., NW, Washington 6, D.C. The application deadline is *1 December,* and successful candidates will be notified by 1 March 1959.

Geographic field research. The National Academy of Sciences–National Research Council will conduct, in 1959, under the financial sponsorship of the Office of Naval Research, its fourth annual program of geographical field research in foreign areas.

The objective of the program is to strengthen American Geography by stimulating greater participation by young Americans in field research in areas outside of the English-speaking areas of North America. Support will be made available not only to young geographers but also to young scientists in related fields, such as geomorphology, climatology, ecology, and pedology.

The program is designed primarily for graduate students who wish to conduct field research in connection with their doctoral dissertations, but persons who have received the doctorate within the last few years are also eligible.

The extent of financial assistance will vary according to the needs involved. The intent is to provide adequately for travel, field, and living expenses. Usually no stipend is provided. A preference will be shown for field investigations of at least 6 months duration, preferably a year or more.

Applications for support of field work which is to be initiated before 1 April 1960 must be submitted prior to *1 December 1958.* Applications and requests for further information should be addressed to Foreign Field Research Program, Division of Earth Sciences, 2101 Constitution Ave., Washington 25. D.C.

Scientists in the News

KEITH GLENNAN, president of Case Institute of Technology and former member of the Atomic Energy Commission, has been nominated by President Eisenhower to head the National Aeronautics and Space Administration. HUGH L. DRYDEN has been named as deputy administrator. Dryden is director of the National Advisory Committee for Aeronautics, which will be the nucleus of the new civilian space agency.

Six prominent scientists will give a series of evening lectures at the second United Nations International Conference on the Peaceful Uses of Atomic Energy, which will begin on 1 September in Geneva. The lectures are open to the public. They will be given on three evenings during the 2-week conference, with two speakers scheduled for each evening.

On 5 September the first lecture will be delivered by HOMI BHABHA of India, who was president of the first International Conference in 1955. He will speak on the role of nuclear power in the underdeveloped countries. On the same evening J. E. TAMM of the U.S.S.R. will speak on recent developments in the field of fundamental physics. On 10 September GLENN T. SEABORG of the United States will give a lecture on recent developments in the field of the transplutonic elements. This will be followed by a lecture by V. A. ENGELHARDT of the Soviet Union on the implications of atomic energy in the field of biology. The last set of evening lectures will be given on 12 September. LLOYD V. BERKNER of the United States will speak on international collaboration in science, and JOHN COCKCROFT of the United Kingdom will give a survey of the conference in a lecture on trends in the development of peaceful uses of atomic energy.

WALTER A. MACLINN, chairman of the department of food science at the Agricultural Experiment Station, Rutgers University, has resigned to become director of the Refrigeration Research Foundation, Colorado Springs, Colo. His new responsibilities will include the stimulation and encouragement of refrigeration research in university and other laboratories.

JOHN S. BOYCE, professor emeritus of forest pathology at Yale University, has been named director of the Bartlett School of Tree Surgery, Stamford, Conn. He succeeds the late Sherman P. Hollister, professor emeritus of horticulture at the University of Connecticut.

STANLEY S. BALLARD, research physicist at the Scripps Institution of Oceanography of the University of California, has accepted the position of professor of physics and chairman of the department of physics at the University of Florida in Gainesville, effective this fall. He will continue his activities as vice president for meetings of the Optical Society of America and executive secretary of the Armed Forces–National Research Council Committee on Vision.

WILLIAM F. MEGGERS, chief of the spectroscopy section of the National Bureau of Standards, retired on 31 July after 44 years of continuous service with

the bureau. Megger's work has been concerned chiefly with standard wavelengths in optical spectra, descriptions of atomic and molecular spectra, spectroscopic light sources, Zeeman effect, analysis of spectral data for the derivation of atomic energy levels, atomic structure, and properties of atomic nuclei. Probably his outstanding achievement has been the development of the mercury-198 lamp, which gives off a green spectral line so pure that its wavelength can be determined to one part in one billion.

Meggers has received a number of awards, including the Frederic Ives Medal of the Optical Society of America, a special award of the Society for Applied Spectroscopy for "outstanding accomplishments in the field of atomic spectra," the Franklin Institute's Elliot Cresson Medal, the Department of Commerce gold medal for exceptional service, and a recognition medal from the University of Liège. Meggers has also held top offices in various technical societies. He has been president of the Optical Society of America, president of Commission 14 of the International Astronomical Union, chairman of the National Research Council Committee on Line Spectra of the Elements, vice president of AAAS Section B, and president of the International Joint Commission for Spectroscopy.

Meggers received his B.A. in physics from Ripon College in 1910, his M.A. in physics from the University of Wisconsin in 1916, and his Ph.D. in physics, mathematics, and astronomy from Johns Hopkins University in 1917. He joined the NBS staff in 1914, and was made head of the spectroscopy section in 1920.

J. O. IRWIN, member of the Medical Research Council of Great Britain's Statistical Research Unit, London School of Hygiene and Tropical Medicine, will spend this academic year as visiting professor in the department of biostatistics at the School of Public Health, University of North Carolina, Chapel Hill.

Another visitor from Great Britain is J. H. RENWICK, member of the Medical Research Council's Population Genetics Research Unit, London. He will conduct research in the department of medical genetics, Johns Hopkins Hospital, Baltimore, Md., from 1 October to the end of the year.

CHARLES HUGGINS, director of the Ben May Laboratory for Cancer Research of the University of Chicago, recently received the Charles Mickle fellowship of the University of Toronto for the year 1958 for "his contributions in the field of cancer." The award is made to that member of the medical profession and related sciences who is considered by the Council of the Faculty of Medicine of the University of Toronto "to have done most during the preceding 10 years to advance sound knowledge of a practical kind in medical art or science."

Huggins has also received the £300 Cameron Prize of the University of Edinburgh. This prize is awarded biennially to a "person who, in the course of the five years immediately preceding has made any highly important and valuable addition to Practical Therapeutics." Huggins was honored for his research on the hormonal treatment of cancer.

JOSHUA LEDERBERG, chairman of the department of medical genetics at the University of Wisconsin School of Medicine, has been named to head a new department of genetics at Stanford University School of Medicine, effective in April 1959.

HAROLD LYONS, head of the atomic physics department of the Hughes Aircraft Company, Culver City, Calif., will receive a Certificate of Merit from the Franklin Institute on 15 October. He is being honored for "his work in pioneering the development of clocks of very great precision based on the natural periods of vibration of atoms and employing microwave techniques."

Recent Deaths

LUDWIG ADLER, New Milford, Conn.; 82; senior gynecologist and obstetrician at St. Clare's Hospital and a practicing physician in New York until his retirement 2 years ago; professor of gynecology and obstetrics at the University of Vienna and director of the gynecological department of the Empress Elizabeth Hospital, Vienna, Austria, before coming to the United States in 1938; 8 Aug.

MANOEL F. DE MAYO BEHAR, New London, N.H.; 69; vice president of the Instrument Publishing Company, Pittsburgh, Pa., and editor of *Instruments Magazine*, 1929–55; 1 Aug.

CHARLES B. BREED, Camden, Me.; 82; head of the civil engineering department of Massachusetts Institute of Technology, 1935–45; professor of railroad and highway transportation at the institute, 1906–45; 9 Aug.

HAROLD W. BUCK, Greenwich, Conn.; 85; electrical engineer; directed the Niagara Falls electrical power project, 1900–10, and thereafter the Victoria Falls power project in Rhodesia; 5 Aug.

EMMETT K. CARVER, Rochester, N.Y.; chemist and technical assistant to the general manager of Kodak Park Works, Rochester, N.Y.; former instructor in physical chemistry at the University of Illinois; 26 July.

GEORGE W. CLAPP, New Rochelle, N.Y.; 87; former technical and educational director of the Dentist Supply Company of New York; author of many books on dentistry and former editor of *Dental Digest*; 8 Aug.

GEORGE H. COLLINGWOOD, Washington, D.C.; 67; conservationist and head of the Natural Resources Section, Legislative Reference Service of the Library of Congress; former chief forester of the American Forestry Association; professor of forestry at New York State College of Agriculture, 1916–23; 7 Aug.

GEORGE E. CONDRA, Glendale, Calif.; 89; dean emeritus of conservation and soil survey, University of Nebraska; had been associated with the university's geology and geography department for 50 years; 7 Aug.

HAL D. DRAPER, SR., Nevada City, Nev.; 64; chairman of the division of science and mathematics and professor of chemistry at Sacramento State College since 1948; had taught at the University of California, Rice Institute, Fresno and Chico State College, and Sacramento Junior College.

WILLIAM DURAND, New York; 99; engineer and former head of the department of mechanical engineering at Stanford University; principal of the Graduate School of Marine Engineering and Naval Architecture at Cornell University in 1891; contributed to the early development of hydrodynamics and aerodynamics; author, beginning at the age of 68, of the six-volume *Aerodynamic Theory*; 9 Aug.

MARCEL GOLDENBERG, New York, N.Y.; 57; heart specialist and assistant clinical professor of medicine at Columbia University College of Physicians and Surgeons; discovered noradrenalin, which is used to maintain normal blood pressure in surgery; 30 July.

FRANK GROUT, Minneapolis, Minn.; professor emeritus of geology, University of Minnesota, and former director of the Minnesota Geological Survey; 1 Aug.

LIONEL C. RUBIN, New York, N.Y.; 53; former associate clinical professor of dermatology at the New York University–Bellevue Medical Center; 6 Aug.

HELEN K. STEWARD, Washington, D.C.; chief of the editorial office of the Armed Forces Institute of Pathology; 9 Aug.

EDWIN SUTERMEISTER, Westbrook, Me.; 81; retired chief research chemist of the S. D. Warren Company; specialist in paper making; 30 July.

WINSTON H. TUCKER, Evanston, Ill.; 57; Public Health Commissioner; performed research on the effects of fluorine in drinking water that led in 1947 to the addition of fluorine to the Evanston water supply (7 years later he reported that tooth decay in Evanston children had decreased by 56 percent); 3 Aug.

Book Reviews

Dynamics of Behavior. Robert S. Woodworth. Holt, New York, 1958. x + 403 pp. Illus. $5.

"The main contention of this book—seemingly a perfectly obvious and innocent view—is that behavior consists of active give and take between the organism and the objective environment. This interrelationship may be called dealing with the environment."

This short passage, in Woodworth's clear style, is the keystone of a systematic structure of psychology built through many years and presented now in fairly complete form. The statement does seem "obvious and innocent," but it tells a good deal.

In writing a general psychological theory some authors choose a "tight" system with few independent principles and many specific deductions. Others favor a more flexible scheme, with principles which are very general and have little specific implication. The first approach risks being wrong, the second, being vague. C. L. Hull, of whom Woodworth often makes telling criticisms, chose the first plan. Woodworth himself, more empirically inclined, takes the latter. The broad statement quoted tells us that behavior will not cease when the biological needs are satisfied, for there are many interactions with the environment which are primary and not derived from needs. The facts arrayed to support this are powerful. Yet the proposition does not attempt to say what objects will be "dealt with" or to state the manner of the dealing. These matters would remain, presumably, as unsystematized observed facts.

"Objects" is an important word in the statement. These lasting collections of physical properties and relations, rather than simple stimuli, are the whence and whither of behavior. Therefore there needs to be, Woodworth contends, an encoded representation of these built up in the organism, a "perception" of the environment. The most important sort of learning, if not all of it, is the learning of places, distances, and other sorts of relation, rather than the connecting of movements with stimuli.

One may also read the book as a survey and discerning critique of experimentation—much of it very recent, some of it classic, and some older but little known. This will surely cause the book to be widely studied, and the theoretical interpretation will as surely make it widely discussed. It could hardly be otherwise with a book by R. S. Woodworth.

R. C. Davis
Department of Psychology, Indiana University

Mass Spectroscopy. Henry E. Duckworth. Cambridge University Press, New York, 1958. xvi + 206 pp. Illus. $6.50.

This newest addition to the *Cambridge Monographs on Physics* is a rapid scan over the spectrum of instrumental principles and physical applications of mass spectroscopy. It is not a "do-it-yourself" handbook, and it does not provide a detailed discussion of instrumental and vacuum techniques and chemical applications. Duckworth's book is more a *Reader's Digest*-type summary, in which the brevity and restriction of subject matter reflect the evolution of the mass spectrometer from the demimonde of development to the social whirl of everyday research.

The first half of the book covers ionic focusing, production and detection of positive ions, and the various kinds of mass spectroscopes, from simple direction focusing to double focusing, time-of-flight, and cyclotron resonance instruments. The treatment is authoritative, factual, and succinct, with the emphasis on actual numerical data on performance and design parameters. A general acquaintance with orthodox instrumentation and electronics is assumed, and derivations of equations are generally omitted; granted these premises, what is left is a highly condensed and well-organized summary of essential facts and references.

The remainder of the book is devoted to isotopic abundance and atomic mass determination, applications to nuclear physics, ionization and dissociation of molecules, and applications to geology. Some 25 pages are given to geological studies on radiogenic and stable isotope variations, but only the briefest survey of these rapidly expanding fields was possible in that space. [The citation of Nier's standard carbon isotope ratio (page 168) should give limestone, rather than sandstone, as the material analyzed.] A table of isotopic abundances and atomic masses, and 16 pages of references, conclude the book.

The discussion of atomic masses is of special interest because of the increasing awareness that O^{16} and $O^{(16+17+18)}$ are hardly suitable mass standards in this day and age. The author shows considerable restraint, for a mass spectroscopist, in his discussion of the mass scales, but he does indicate the importance of adopting C^{12} as a universal mass standard, emphasizing the general agreement on the C^{12} mass spectrometric mass and its unmatched utility as a standard for atomic masses. The discussion of this subject could and should have been amplified considerably; reticence on a controversial subject is unbecoming to an authority. The recent discovery by Mattauch that the discrepancies between mass spectroscopic and nuclear reaction mass data generally disappear if any standard other than O^{16} is chosen adds considerable fuel to the C^{12} fire. It does seem that chemists might be sufficiently involved in physics these days to give up their sentimental attachment to the analytical balance; and, who knows—if we can abolish the double standard for atomic weights we may even hope to get the United States on the metric system some day.

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Cunningham's Manual of Practical Anatomy. vol. I. General introduction. Upper limb, lower limb. Revised by James Couper Brash. Oxford University Press, New York, ed. 12, 1957. xii + 2394 pp. Illus. $6.

Since the 1890's the various editions of *Cunningham's Manual* have led innumerable students through countless dissections. The present 12th edition, the fourth by the same author in the last 20 years or so, attests to the conservative character of the manual. Only volume 1 is as yet available; a few new illustrations, a few new x-rays, and an adaptation to the recently modified terminology of the Paris revision (1955) represent the major changes from the preceding editions.

The text is as simple and direct as ever, the illustrations are clear and diagrammatic, the dissection procedure and precautions are nearly foolproof, and the

scope covers the essentials necessary for medicine and surgery. Practitioners reviewing their anatomy, and students, should find the book as usable as it has always been.

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A History of Mathematics. From antiquity to the beginning of the nineteenth century. J. F. Scott. Taylor & Francis, London, 1958. xiii + 266 pp. Illus. + plates. 63s.

A one-volume history of mathematics cannot be exhaustive, and in the selection of his material the author is likely to betray his predilections. Scott evidently prefers algebra and analysis to geometry, for over half a dozen pages are assigned to Bhaskara—more than the length of the entire chapter on the "Beginnings of modern geometry." There is evident as well a penchant for the enumeration of details of notation and methods, as over against an analysis of the growth of ideas; this explains, perhaps, an occasional lapse in historical-mindedness. For example, the assertion (page 115) that during the first half of the 17th century "there appeared an entirely new creation, namely the study of probability," is belied by the earlier statement (page 92) that in Cardan's *De ludo aleae* "the beginnings of the theory of probability are plainly discernible." Again, Scott accepts (page 129) Lord Moulton's claim that "the invention of logarithms came on the world as a bolt from the blue," despite the history of prosthaphaeretic methods and of relations between geometric and arithmetic progressions. And unconcern for continuity of tradition is aggravated by an unconventional arrangement in which chronological order sometimes is rudely violated. Thus "Mathematics in the Orient" *follows* the account of Hindu and Arabic trigonometry and the Latin medieval period.

The reader with a sense of proportion will be prepared for some inaccuracies in such a work as this. Scott attributes first to Plato (page 20), later to Brahmagupta and Mahavira (page 74), a routine method for Pythagorean triads which is but a special case of a device used earlier by the Babylonians, and he describes Heron's algorithm for square roots (page 42) with no indication that it had been known before in Mesopotamia. The undervaluation of pre-Hellenic mathematics may be an outcome of a handicap under which the author seems to have worked—a heavy dependence upon older secondary sources, such as Cantor rather than Neugebauer on the origin of sexagesimal numeration and Child rather than Hofmann on the calculus priority controversy. There is, on the other hand, a laudable reference, especially for British mathematicians, to important primary sources.

The author's reputation was established years ago through his *Mathematical Work of John Wallis* (1938) and his *Work of René Descartes* (1952), and the present volume is entitled to a comparable place of honor on library shelves. Every here and there Scott affords us commendable new emphases, such as the prominence given to the nongeometrical portions of Euclid's *Elements* and to ancient trigonometry. Noteworthy also are sections on the theory of numbers (including the summary of Gauss's *Disquisitiones Arithmeticae*) and on Newton's use of the binomial theorem for fractional exponents. It will be a crotchety reader indeed who fails to find a quota of sections to his fancy, and the physical appearance of the volume should appeal to the meticulous booklover.

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Adventures in Medical Education. A personal narrative of the great advances in American medicine. G. Canby Robinson. Published for the Commonwealth Fund by Harvard University Press, Cambridge, 1957. xii + 338 pp. Plates. $5.

In the course of a long and distinguished career as a medical educator and administrator, G. Canby Robinson has actively participated in many of the fundamental changes that have revolutionized American medical schools, and along with them medical research and practice, during the present century. Robinson entered the Johns Hopkins Medical School as a student in 1899, six years after it opened, when that school, and a few others, were spearheading the reform to come. In 1910, the year that Abraham Flexner published his shattering analysis of American medical schools, Robinson joined the first staff of the Rockefeller Institute Hospital. Three years later he became a member of the faculty of Washington University Medical School in St. Louis, during the period of its reorganization. In 1920 he became dean of the School of Medicine at Vanderbilt University, where he directed the reorganization of that school, and in 1927 he accepted a post as head of the New York Hospital–Cornell Medical College center, which was also to undergo reorganization. Here, however, Robinson ran into difficulties, which he attributes primarily to the financial crisis caused by the depression and to inadequate organizational integration between the hospital and the college, compounded by the selfishness and antagonism of some of the faculty. Virtually forced to retire in 1934, Robinson returned to Baltimore for work on the social aspects of medicine and, subsequently, on the organization of the wartime blood donor service. However useful this work, the later phases of his career inevitably form an anticlimax.

It is clear from this brief recital that Robinson has had an unusually full opportunity to study medical education in all its aspects. He has undoubtedly been motivated by the highest ideals. His observations therefore deserve attention. He stresses, for example, the importance of opportunities for full-time clinical teaching and research—a view that needs frequent restatement in the face of continuing opposition—and his book further illustrates this point by citing the number of men from the Rockefeller Institute and Johns Hopkins—pioneers in full-time clinical teaching and research—who were involved in the reorganization and reform of other medical schools after 1910.

Nevertheless, I must confess to some disappointment in the book. Robinson's style of writing, while clear, lacks vigor, and, more important, too much has been left unsaid. Robinson was involved in two really significant controversies in his career, one at Vanderbilt and one at Cornell, yet neither is adequately described or explained. The conflicts and therefore the drama in Robinson's career have largely been omitted. What remains is an incomplete account of an important career—an account less human and less interesting than it might have been, but useful nevertheless to medical historians and educators for the comments on men and events and for what it reveals of Robinson's own personality. Perhaps the kindly spirit that has prompted him to minimize the conflicts in this autobiography helps to explain his failures as well as his successes.

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Nature Is Your Guide. How to find your way on land and sea by observing nature. Harold Gatty. Dutton, New York, 1958. 287 pp. Illus. $4.95.

It is a shattering experience for an individual or group of individuals to be lost in the out-of-doors with no assurance of what to do to remedy the situation. The purpose of this book is to help the traveler who may be concerned

with finding his way by recounting the many aids that Nature offers. By learning to recognize these natural aids, it is possible to use them as guideposts in pathfinding in remote places.

The author discusses the methods of navigation employed by the early explorers and primitive races who had few, if any, mechanical aids and depended largely on observing natural phenomena. These methods may be employed today in locating position and direction. On the sea, in addition to the position of the fixed stars as direction guides, the author describes the kinds of clouds and their relation to unseen islands. He shows how the characteristics of the winds, the waves, the swells, the migration routes of birds, and even the odors encountered may be significant aids to navigation.

On land, the effects of sun and wind on snow, sand, vegetation, and animal or insect habitats, such as ant hills, are as important to observe as the contours of the hills, direction of water courses, and other natural guides. Keen perception of the stimuli of the five senses and experience in interpreting these stimuli can convey the impression of a mysterious sense of direction in an individual so schooled. However, the author rejects the theory of any such sixth sense.

This is a fascinating as well as an instructive book. In the 25 chapters the almost countless problems involved in successful route-finding over water and snow, in forests, deserts, mountains, and even in cities, are presented. Of special interest are the chapters devoted to the habits of sea birds.

A foreword to the book has been written by Lieutenant General J. H. Doolittle, who recounts the many years of service that Harold Gatty rendered to the U.S. Army Air Corps when he was in charge of air navigation research and training.

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Kurds, Turks and Arabs. C. J. Edmonds. Oxford University Press, London, 1957. 435 pp. Illus. $6.75.

The expectant reader will find very little here concerning Turks and Arabs —hence the title, while perhaps well meant, is somewhat misleading. However, there are many data about the Kurds, a people on whose history and culture Edmonds is a recognized authority. We are treated to a discussion of "politics, travel and research in northeastern Iraq 1919–1925," and of events in southern Kurdistan impinging heavily on the Mosul question, involving Great Britain–Iraq and Turkey. Edmonds was political officer in the disputed Mosul province.

C. J. Edmonds is one of those dedicated British civil servants who has given the best years of his life in the service of his country abroad, spending the greater part of his fruitful career in Iraq. In its discussion of the events leading up to the Mosul question, the book is extremely useful for its presentation of the British point of view, as seen through the eyes of one of the principals. Edmond's expert opinion made him a logical member of the Anglo-Iraqi delegation on the commission appointed by the League of Nations to investigate the dispute and to recommend a solution. Contrary to a statement made by another author—and incorporated in this book (page 434, footnote)—to the effect that the strong vested interest of the British in the oil of Iraq was a major factor in the decision, one is surprised to note Edmond's reflection that oil was not a matter of "outstanding importance" at the settlement of the Mosul dispute. At any rate, it is to be credited to the British that, through their influence, Mosul was not separated from the Baghdad and Basra provinces—a circumstance which made the state of Iraq a viable entity. Edmonds, who was adviser to the Ministry of Iraq from 1935 to 1945, has supplemented his field knowledge with the temper of time and perspective. One regrets that he could not bring us up to date on events which figure so much in the current dispatches.

Scholarship and mastery of source material are evident in this book. There is a fund of bibliographic references for the student to check for himself. Drawing upon personal diaries and documents available to him, Edmonds pays fine attention to details. Antiquities and archeology, ethnographic history, genealogy, geography, politics, and intrigues are all interwoven into a delightful mélange. And when the reader tires of the recitation of journeys through endless strangely named villages and ranges, he will be able to find diversion in Edmond's translations of Kurdish poems, each one a treasure.

In relentless pursuit of law and order, the indefatigable political officer was equally at home in the saddle or in the slip stream in an open cockpit. We are amazed at his account of the Hollywood-like escapades of a particularly unruly Kurdish sheikh from Sulaimani, who on one occasion absconded with the treasury, the municipal printing press, and a body of native troops in order to wage a personal propaganda war for independence. This thorn in the British side always managed to escape when the net grew too close for him or when the punitive airplane bombings proved especially distracting. Interspersed in Edmond's account are nostalgic memories of holiday parties and hunts that tided him over the duller moments.

One receives the impression that Edmonds has pulled together his past published material for this work, with new additions, and that this offering is his last word on the subject. Let us hope that this latter is not true, and that we shall hear more from him soon.

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Physik und Technik der Atomreaktoren. Ferdinand Cap. Springer, Vienna, Austria, 1957. xxix + 487 pp. Illus. $15.25.

This is a first attempt to publish in the German language a book covering the entire subject of reactors from the point of view of physics and engineering. The book is based on lectures given by Cap at the University of Innsbruck (Austria). The level of the book lies somewhere between that of a textbook for students of reactor engineering and a source book for specialists. It will serve as an introduction to the subject, but the serious student will find it necessary to refer to the original literature. The extensive bibliography will aid him in such efforts. Many problems are offered at the end of each of 49 sections. The loose enclosure of four pages of corrections will give the reader satisfaction if he is hunting for further misprints.

In chapter 1 the fundamental aspects of nuclear physics are presented: the mass formula of Bethe and Weizsaecker, a treatment of radioactive decay, nuclear reactions, the Breit-Wigner formula, cross sections, neutron physics, fission, and fusion of nuclides.

Chapter 2 is devoted to a description of the energy losses of neutrons, elastic and inelastic scattering, energy distribution after a collision, slowing down in hydrogen and other materials, influence of resonances and temperature, and neutron chain reactions.

Chapter 3 discusses the theory of neutron diffusion. Transport theory is used only in the introductory section of the chapter and for improvement of more approximate results. Two sections about diffusion with slowing down and Fermi age theory close this chapter.

From chapter 4 on, the book deals with reactor applications. Homogeneous reactors are dealt with in chapter 4. Some of the topics offered are the critical volume of a one-group reactor, its criticality equation, reactors of different shapes, multigroup theory, influence of a reflector, dynamical behavior of re-

actors, their period and oscillations, and prompt and delayed neutrons.

Chapter 5 covers the theory of the heterogeneous reactor. The construction of reactors with different kinds of fuels, moderators, reflectors, and heat transport is discussed in chapter 6. Reactor operation and control and the burning up and poisoning of the fuel (and its regeneration) are the topics dealt with in chapter 7. Several types of reactors are described in chapter 8—especially light and heavy water as well as graphite moderated reactors. A survey of the use of reactors for research, education, and medical applications, for the production of fuel, isotopes, energy, and propulsion, and for industrial purposes is given in chapter 9. This chapter closes with a discussion of questions of law and organization.

Tables of contents, tables, figures, a glossary of symbols, and a large index are included.

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Reports

Calcium Phosphate Sequestering Phosphopeptide from Casein

By the use of ion-exchange columns, a number of crude phosphopeptide fractions have been separated from pancreatic casein hydrolyzates. One of these fractions exhibits, to a remarkable degree, the property of sequestering calcium phosphate in the *p*H range from 7 to 10.5. Although numerous investigations have been made on phosphopeptides derived from casein by various enzymatic hydrolyses (*1*), no mention of this calcium phosphate sequestering property has been found in the literature.

The finding of a casein fragment with the property of solubilizing calcium phosphate, or preventing its precipitation at relatively high *p*H's, has obvious implications in regard to an understanding of the role of casein in calcium and phosphate transport and assimilation. Apart from its interest in this connection, the phosphopeptide is of practical use in preventing the formation of calcium phosphate precipitates in culture media containing relatively high concentrations of phosphate and calcium ion.

Eighteen grams of the calcium phosphate sequestering phosphopeptide were obtained from 2 lb of Trypticase, a pancreatic casein hydrolyzate (*2*). The Trypticase was dissolved in 18 lit. of a buffer containing 0.1*M* sodium acetate and 0.1*M* acetic acid. This solution was passed through a 4- by 45-cm column of Dowex-1 (Cl form, 50 to 100 mesh). The column was washed with 16 lit. of the same buffer until the free amino acids, neutral peptides, and the inorganic phosphate had been removed. Since these operations require several days for completion, they were conducted in a cold room to avoid microbiological action. When negative tests for inorganic phosphate were obtained on the effluent solution, the column was removed to the laboratory and elution was begun with 0.05*N* hydrochloric acid. The eluant removed a large phosphopeptide fraction which was poor in calcium phosphate sequestering power. The peak of this fraction appeared in the 15th liter of eluant, and it dropped off rapidly thereafter. After 18 lit. of the dilute acid had been passed the concentration of hydrochloric acid was increased to 0.3*N*, and the active phosphopeptide was obtained in the next 2 lit. of eluant. It was isolated as its calcium salt by neutralization to *p*H 7 with sodium hydroxide, addition of 30 g of calcium chloride, and precipitation with three volumes of alcohol. The precipitate was collected by decantation and centrifugation, and it was washed successively with alcohol, acetone, and ether. After it had been dried in a vacuum desiccator at room temperature, the precipitate retained 12 percent of volatile solvent which could be removed by drying to constant weight at 100°C in high vacuum over P_2O_5.

Analyses on this preparation of calcium phosphopeptide were: N, 9.9; P, 6.6; Ca, 12.2. The optical rotation in water was $[\alpha]_D^{25} = -67.5°$. The preparation contained no inorganic phosphate.

The calcium phosphate sequestering power of the calcium phosphopeptide is illustrated by the following experiments. Four hundred and forty milligrams of the anhydrous calcium salt were dissolved in 10 ml of 0.1*M* phosphate buffer at *p*H 7. To this solution was added 1 ml of 1*M* calcium chloride solution. There was no turbidity or precipitation in the solution. By cautious addition of normal sodium hydroxide with stirring, the *p*H was increased to 10.5 without the appearance of turbidity. After the solution was adjusted to *p*H 9, it was boiled and allowed to stand in the refrigerator for 2 months; during this time no turbidity or precipitation occurred.

In a second experiment the ability of the peptide to dissolve precipitated calcium phosphate is illustrated. To a solution containing 100 μmole of phosphate in 0.1*M* trihydroxymethylaminomethane was added 150 μmole of calcium chloride. The final volume was 10 ml, and the *p*H was 8.5. Upon analysis after centrifuging it was found that 5 μmole of phosphate remained in the supernatant solution. Forty-four milligrams of the calcium phosphopeptide were stirred into the suspension of calcium phosphate, and centrifuging was repeated after 20 minutes. It was found that the solution contained 15.5 μmole of inorganic phosphate. The precipitate was again stirred and allowed to stand for 7 hours at room temperature, at which time 46.3 μmole of the phosphate were found to be in solution. Since inorganic phosphate of the peptide is not liberated by standing at room temperature at *p*H 8.5, the dissolved phosphate must have come from the calcium phosphate which had been precipitated in the first step of this experiment.

Under conditions favorable for calcium phosphate sequestering—that is, *p*H 7 to 9 and no great excess of either calcium or phosphate ion—the calcium phosphopeptide will sequester two-thirds of its weight of calcium phosphate (calculated as $CaHPO_4$) and hold it in solution through boiling or autoclaving. At room temperature and *p*H 9 it will hold in solution about one-half its weight of calcium phosphate in the presence of a 50-fold excess of either calcium or phosphate ion.

In other work (*3*) it has been learned that the calcium phosphate sequestering power is associated with material which migrates rapidly toward the anode upon electrophoresis on paper at *p*H 4.1 (phthalate buffer). The calcium phosphate sequestering property of the phosphopeptide is destroyed by acid or alkaline hydrolysis or by the action of phosphatases.

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3. A paper describing this work is in preparation.

2 April 1958

Radiocarbon Dating Up to 70,000 Years by Isotopic Enrichment

Isotopic enrichment of radiocarbon is an obvious method for dating samples which are too old and therefore have too small an activity. Enrichment by a factor of 2^n shifts the limit of counting by n half-lives. The amount of enriched material is fairly large, however, and this leads to considerable technical in-

All technical papers are published in this section. Manuscripts should be typed double-spaced and be submitted in duplicate. In length, they should be limited to the equivalent of 1200 words; this includes the space occupied by illustrative or tabular material, references and notes, and the author(s)' name(s) and affiliation(s). Illustrative material should be limited to one table or one figure. All explanatory notes, including acknowledgments and authorization for publication, and literature references are to be numbered consecutively, keyed into the text proper, and placed at the end of the article under the heading "References and Notes." For fuller details see "Suggestions to Contributors" in *Science* 125, 16 (4 Jan. 1957).

vestments: the large counter in operation in Groningen requires 8 liters of CO_2. A sample enriched 16 times contains as much C^{14} as 128 liters of the original material. Since the depletion of the reservoir should be at most about 30 percent in order to avoid an appreciable decrease in the transport of C^{14}, about 350 liters of sample are required at the least.

The enrichments are performed at the Laboratory for Mass Spectrography in Amsterdam. The CO_2 obtained from the original material (*1*) is reduced to CO by leading it over zinc at a temperature of 380° ± 5°C. The CO is enriched in five thermal diffusion columns connected in parallel, each of them having a length of 430 cm. The enrichment is derived from the O^{18} abundance in the CO (*2*). For the activity measurements, the enriched CO is oxidized again by leading it over CuO. Enrichment by a factor of 16 takes at present about 2 months; this enrichment shifts the limit of counting to about 70,000 years.

Up to now three samples have been measured. The first sample consisted of recent carbon dioxide diluted with a known amount of inactive CO_2. The enrichment predicted by the abundance of O^{18} was 8.70 ± 0.5; the enrichment measured was 8.06 ± 0.05.

The second sample consisted of dead CO_2 (from anthracite). If all steps are completely free from contamination by recent carbon, the enriched sample should still be inactive. The activity was actually 0.04 ± 0.02, corresponding to an apparent age of 73,000 years. The activity is not really significant, however. This experiment will be repeated in due course.

The third sample consisted of wood from a well-exposed profile at Amersfoort (Netherlands). The situation has been described in more detail by H. de Vries (*3*); it is indicated as Amersfoort XII. The present sample dates the end of the Last Interglacial or an early Würm interstadial separated from the Last Interglacial by a not very cold period. The age found by enrichment was 64,000 ± 1100 years (sample Gro-1397). The limits of error include the statistical error only. Errors introduced by the enrichment and measurement of the enrichment amount to about 800 years. The most important source of error, however, for these old samples is infiltration of recent material (see also *3*). The wood had been cleaned thoroughly by chemical treatment. Humus extracted from it has an age of 42,300 ± 900 years only. So even this wood, protected by a shield of compressed peat and 9 meters of sand, had acquired some recent hume (the extracted humus is a mixture of original material and infiltrated material). Because of possible infiltration, all dates are more or less minimum dates, but our opinion is that the present date is fairly reliable. It fits fairly well with the chronology developed by de Vries (*3*, *4*).

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28 March 1958

Extending the Range of Dose-Effect Curves for Irradiated Mice

A recurring problem in experiments yielding results to be expressed in the form of dose-effect curves is the need to use responses measured in different units at different parts of the dosage scale. Any attempt to combine two such responses rests on the assumption that they reflect the same phenomena. A number of methods for extending the dosage scale by combining percentage survival and survival time into a single response have been proposed (*1*). We report here a simple method for combining information on survival which we have recently found useful in our studies on the effect of colchicine and its derivatives in irradiated mice (*2*).

When given 24 hours before exposure to radiation which would kill all controls in an average of 9 days or longer, trimethylcolchicinic acid methyl ether d-tartrate increased the percentage surviving. When given to animals which radiation would kill in 8 days or less, no effect on survival was obtained. After the results were plotted in the usual way (upper half of Fig. 1*A*), the ordinate at zero survival was equated with the mean survival time of the animals which had received the lowest radiation dose required for approximately zero survival (in these experiments, 1000 r and 10.5 ± 0.6 days). At higher radiation doses, survival time gradually decreases to a plateau value of approximately 4 days (*3*). It was noted that this plateau was reached at a radiation dose which is the same distance above the approximate LD_{100} as the dose which would kill almost no animals is below the LD_{100} (1300 r, 1000 r, and 700 r). The ordinate was extended downward to 4 days, and the distance between 4 and 10.5 days was made to equal the distance between 0 and 100 percent survival, with the LD_{100} becoming, on the combined scale, the mid-dose, which for a single response would be the ED_{50} (lower half, Fig. 1*A*). The data, when plotted in this way, yield a smooth radiation dose-effect curve, permitting an expression of percentage mortality and mean survival time

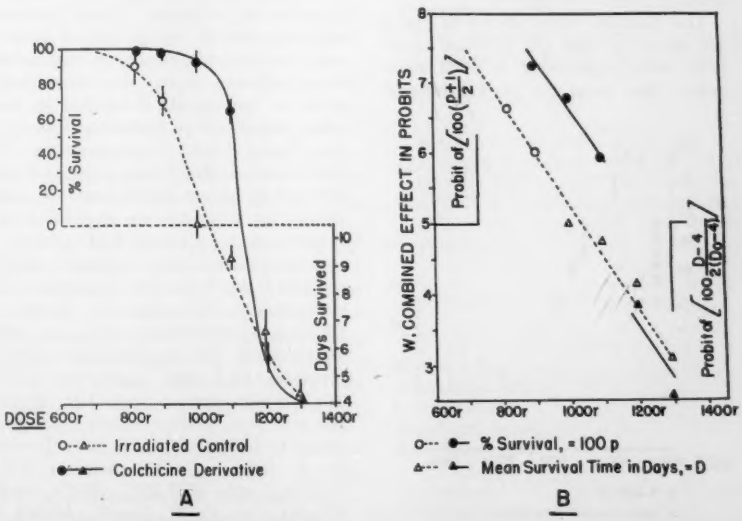

Fig. 1. (*A*) Plot of percentage survival and mean survival time by radiation dose for control mice and those treated with a colchicine derivative (1 mg of trimethylcolchicinic acid methyl ether *d*-tartrate, administered intraperitoneally 24 hours before irradiation). (*B*) Same data plotted in probits.

in a unit which bears a simple relationship to dose. It was noted that the combined plot had the general appearance of a sigmoid curve and should therefore be approximately linear on probit transformation (Fig. 1*B*).

In order to test the general applicability of this procedure, control data from all other experiments with the same strain and sex of mice and the same radiation factors (*4*) were compiled and plotted as shown in Fig. 2. Data for survival time could be used for the groups in which fewer than 50 percent survived. The results are essentially the same as those shown in Fig. 1.

A general procedure, therefore, for converting the two responses to the same unit is obtained by defining an effect W (*5*), such that

$$W = \frac{p+1}{2}$$

$$= \frac{D-4}{2(D_0-4)}$$

where p is the proportion surviving, D is the mean survival time, and D_0 is the mean survival time of mice given the minimum radiation required for approximately zero survival.

For many purposes in which graphic analysis is adequate it is sufficient to use the left-hand ordinate for percentage survival and the right hand ordinate for survival time, with the latter so scaled that at zero survival $D = D_0$ and at 100 percent survival $D = 2D_0 - 4$. If a linear dose-response curve is desired W may be plotted on probit paper, but the usual maximum likelihood calculation procedure is not applicable because the standard error of W is not the same as the standard error of an equal p.

The standard errors shown in Fig. 2 are estimated from the variation of results from experiment to experiment rather than from the pooled internal variation. The points representing percentage survival and survival time at the same dose level fall on essentially the same curve. Although some increase in precision could be obtained at these levels by combining the two responses, the simplicity of the procedures involved in using percentage survival alone has much to recommend it.

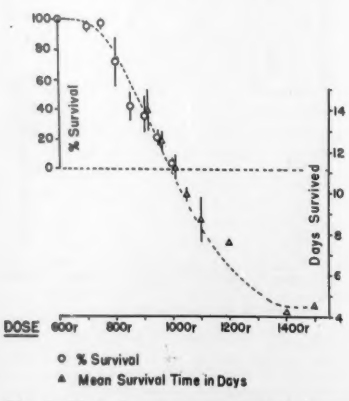

Fig. 2. Plot of percentage survival (open circles) and mean survival time (open triangles) by radiation dose for 66 control groups of mice not represented in Fig. 1.

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4. Mice were (BALB/c × DBA/2)F_1 females 12 to 15 weeks old, kept in individual cages. Irradiation was from a Van de Graaf generator operating at 2.5 Mev, 0.6 HVL 1 cm lead, TSD 1 m, and dose rate 250 to 300 r/min. We are indebted to Dr. Howard L. Andrews for dosimetry and irradiation.
5. For Waldorf.

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Volatile Fatty Acid Growth Factor for Cellulolytic Cocci of Bovine Rumen

The anaerobic cellulolytic cocci belonging to the genus *Ruminococcus* (Sijpesteijn) Hungate (*1*) are considered to be important participants in rumen fermentation because of the large number that are present in the rumen and because of their capability for rapid digestion of cellulose. These bacteria comprise one of the groups of rumen organisms that require or are stimulated by a factor(s) present in rumen fluid which is not usually detectable in the usual ingredients of bacteriological media. Strain C-94, a representative of *Ruminococcus flavefaciens* isolated from 10^{-8} ml of bovine rumen contents, was chosen for this study to determine its requirement for a rumen fluid factor(s).

A basal medium was developed which contained the following substances (in milligrams per 100 milliliters): thiamin · HCl, Ca-D-pantothenate, riboflavin, and nicotinamide, 0.2; pyridoxamine · 2HCl, pyridoxal · HCl and pyridoxine · HCl, 0.1; *p*-amino benzoic acid, 0.01; biotin and folic acid, 0.005; cobalamin, 0.0005; casein hydrolyzate (acid), 200; Tween 80, 4; cellobiose, 300; resazurin, 0.1; Na_2CO_3, 400; KH_2PO_4, NaCl, and NH_4SO_4, 90; $CaCl_2$, $ZnSO_4$, $MgSO_4 \cdot 7H_2O$ and $MnSO_4 \cdot H_2O$, 1; $FeSO_4 \cdot 7H_2O$, 2; $CoCl_2 \cdot 6H_2O$, 0.4; and cysteine · HCl · H_2O, 100. The medium was adjusted to *p*H 6.7 and was sterilized and inoculated under CO_2 by the anaerobic technique of Hungate as used by Bryant and Doetsch (*2*). Additions to the basal medium were separately sterilized and were combined after autoclaving.

Growth was expressed as optical density (OD) as determined with a Bausch and Lomb Spectronic 20 colorimeter at 600 mμ. Inoculum was prepared from a 24-hr culture in a medium containing 20 percent clarified rumen fluid (CRF), and minerals, cellobiose, resazurin, and reducing agent as in the basal medium. The culture was centrifuged, the supernatant was decanted, and the cells were diluted to an optical density of 0.1 with the anaerobic dilution solution of Bryant and Burkey (*3*). Five-milliliter volumes of medium were inoculated with 0.1 ml of the cell suspension. The clarified rumen fluid consisted of supernatant after fresh rumen fluid was centrifuged at 25,000 *g* for 30 minutes.

The basal medium did not support growth of strain C-94 alone or when the following were added: enzymatically hydrolyzed casein; purines and pyrimidines; inositol, choline and sodium acetate; or glutamine, coenzyme I, and glutathione. Clarified rumen fluid and bovine feces extract supported good growth. Polypeptone, trypticase, thiotone, and lactalysate each supported growth in the basal medium, but growth was much delayed compared with that in clarified rumen fluid or feces extract. Crude materials incapable of supporting growth when they were added to the basal medium included peptone, phytone, yeast extract, beef extract, liver extract, corn steep water, distillers' dried solubles, and a hot-water extract of a mixture of alfalfa and brome grass.

It has been shown that certain volatile fatty acids present in rumen fluid are required by a rumen bacterium (*2*). A mixture of known acetate, propionate, *n*-butyrate, isobutyrate, *n*-valerate, isovalerate, DL-α-methyl-*n*-butyrate, and *n*-caproate in proportions similar to those found in rumen fluid supported growth of strain C-94 when it was added to the basal medium. Deletion of acetate from the mixture resulted in a marked increase in the incubation time required to reach maximum growth. When the other acids were added singly in the presence or absence of acetate, only isovalerate and isobutyrate promoted growth. Acetate shortened the lag phase of growth when it was added with these acids. No effect on growth was noted when *n*-valerate was added to the basal medium plus acetate and isobutyrate and/or isovalerate.

Growth in the basal medium with added fatty acids was much less than it was when clarified rumen fluid was present. During a study with various reducing agents it was found that, when Na_2S

Table 1. Effect of clarified rumen fluid, fractions of rumen fluid, and known volatile fatty acids on growth of cellulolytic cocci from the bovine rumen.

Addition to basal medium	Growth of strain (optical density × 100)†				
	7	20	FD-1	B146	C94
	*Experiment 1**				
No addition	0(168)	0(168)	11(123)	14(168)	0(168)
Clarified rumen fluid	69(15)	78(15)	64(15)	72(19)	64(19)
Acid steam distillate	67(19)	83(19)	34(47)	37(30)	53(24)
Residue from acid steam distillate	0(168)	0(168)	16(100)	14(71)	15(168)
Acid steam distillate + residue	70(15)	69(15)	50(19)	63(30)	37(24)
	Experiment 2‡				
Acetate	0(168)	0(168)	12(168)	13(168)	0(168)
Acetate, propionate, *n*-butyrate, isobutyrate, *n*-valerate, isovalerate, DL-α-methyl-*n*-butyrate, and *n*-caproate	75(24)	63(24)	42(48)	32(24)	53(30)
Acetate, isobutyrate, *n*-valerate, isovalerate, and DL-α-methyl-*n*-butyrate	79(24)	66(30)	47(42)	40(19)	60(24)
Acetate, propionate, *n*-butyrate, and *n*-caproate	5(120)	9(120)	13(48)	10(120)	0(168)
Acetate and isovalerate§	64(24)	57(30)	49(42)	29(42)	54(36)

* Levels added were 8 percent of clarified rumen fluid or the amount of the fraction equal to 8 percent clarified rumen fluid.
† The number in parentheses is the number of hours of incubation required to reach maximum growth.
‡ The levels of fatty acids added were the following in millimoles per 100 milliliters: acetate, 4; propionate, 0.13; *n*-butyrate, 0.065; isobutyrate, *n*-valerate, isovalerate, and DL-α-methyl-*n*-butyrate, 0.0128; and *n*-caproate, 0.0064.
§ The level of isovalerate was increased to 0.5 m mole/100 ml.

replaced the cysteine in the basal medium, increased growth was obtained. The precipitate which formed when sulfide was added was eliminated by exclusion of $FeSO_4$, $ZnSO_4$, $CaCl_2$, and $CoCl_2$. This modified basal medium, containing 50 mg of $Na_2S \cdot 9H_2O$ per 100 ml, was used in subsequent experiments and permitted growth with fatty acids approaching that obtained with clarified rumen fluid.

The volatile acid fraction of clarified rumen fluid obtained by steam distillation at *p*H 1.5 supported growth of strain C-94 similar to that obtained by an equivalent concentration of rumen fluid, while the nonvolatile residue did not support growth.

To determine whether other strains of cellulolytic cocci require volatile fatty acids, strains FD-1 and B_1-46 similar to *Ruminococcus flavefaciens* and strains 7 and 20 of *R. albus* (*1*) were studied.

The effect of known volatile fatty acids and fractions of clarified rumen fluid obtained by steam distillation on growth of the five strains is shown in Table 1. All of the strains were markedly stimulated by the steam distillate while the residue contained little or no growth promoting factor(s). The mixture of eight known volatile fatty acids stimulated growth of all strains, as did a mixture of acetate, isobutyrate, and the valeric acid isomers and also a mixture of acetate and isovalerate. A mixture of acetate, propionate, *n*-butyrate, and *n*-caproate contained little growth promoting activity.

The fatty acid growth factor for the cellulolytic cocci appears to be different from that required by the ruminal cellulolytic bacterium, *Bacteroides succinogenes* (*2*). Isovalerate stimulates growth of the cocci, while *B. succinogenes* requires a straight-chain acid such as *n*-valerate or *n*-caproate as well as a branched-chain acid. The factor is also distinct from that required by the *Ruminococcus albus* strain 69 of Fletcher (*4*), which requires a nonvolatile acidic component of rumen fluid. Since all the strains in the present study were greatly stimulated by volatile fatty acids and were isolated from three animals, from two locations, on four different rations, and were selected as representative of both ruminococcus species, it is suggested that organisms with similar nutritional characteristics are quite numerous.

It is now known that strains of three species of bacteria which appear to be among the most numerous and most active cellulolytic bacteria in the bovine rumen require or are greatly stimulated by volatile fatty acids. These findings exemplify the interdependence of rumen microorganisms since the branched-chain fatty acids required by these bacteria are apparently produced from amino acids by other microbial species of the rumen (*5*).

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26 March 1958

Inhibition of Postirradiation Diuresis in Rats by Pitressin

Many observers have reported that total-body irradiation results in an immediate polydipsia and polyuria in the rat (*1–3*). Recent experiments in this laboratory have shown that the thirst and diuresis may be prevented by injection of the antidiuretic hormone after irradiation (*4*).

Fifty-four rats (four adult Sprague-Dawley females and 50 adult Holtzman females) weighing between 150 and 200 g were selected at random from a holding colony. Twenty rats served as controls. The remainder of the rats were irradiated with 1500 r in a Co^{60} facility (*5*) at the rate of 1500 r/min. Within 1 minute after irradiation, the animals were injected intramuscularly by means of a tuberculin syringe and a 22- or 23-gauge needle. Nineteen animals were injected with 500 milliunits of Pitressin tannate (*6*) in 0.1 ml of peanut oil. Fifteen animals received 0.1 ml of peanut oil (*7*). The animals were then placed in individual metabolism cages and allowed free access to tap water but were deprived of food. Water intake and urine output were measured at 24 hours. The results are shown in Table 1.

The irradiated, peanut-oil injected animals exhibited a significant polydip-

Table 1. Average water intake and urinary output per animal during the first 24 hours after 1500 r of Co^{60} irradiation. The number of animals is given in parentheses. All injections were made immediately postirradiation.

Treatment	Water intake (ml)	Urinary output (ml)
Control: fasted, nonirradiated, noninjected animals (20)	10 ± 9	9 ± 5
Irradiated, fasted animals injected with 0.1 ml of peanut oil (15)	55 ± 24	47 ± 21
Irradiated, fasted animals injected with 500 milliunits of Pitressin in 0.1 ml of peanut oil (19)	16 ± 7	7 ± 3

sia ($P < .001$) and a significant polyuria ($P < .001$) compared with the polydipsia and polyuria of the nontreated controls or of the irradiated, Pitressin-injected animals. The urinary output values of the irradiated Pitressin-injected animals were not significantly different from the outputs of the nontreated control animals, but the water intakes were significantly higher than the intakes of the nontreated controls ($.02 < P < .05$). Water intakes and urine outputs within experimental groups were not significantly different in the case of the nontreated controls or the irradiated peanut-oil injected animals. However, water intakes were significantly greater than urine outputs ($P < .001$) in the irradiated, Pitressin-injected group.

These results show that postirradiation polyuria is not due to an obligatory renal tubular water loss, but they do not offer proof for any of the postulated mechanisms. If the phenomenon is the result of an imbalance between adrenal cortical diuretic and posterior pituitary antidiuretic factors as proposed by Smith and Tyree (*2*), the evidence in this paper would suggest that the imbalance can be corrected by the injection of Pitressin.

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24 February 1958

Quantitative Roentgenography of Skeletal Mineralization in Malnourished Quechua Indian Boys

Roentgenograms of the hand suitable for densitometric analysis as well as assessment of skeletal age were taken on 91 Quechua Indian boys from Hacienda Vicos in the North Central Peruvian Sierra. These boys were from a biologically isolated inbreeding population of over 1800 Indians almost wholly unmixed with Europeans (*1*). This Indian population lives in a narrow upland valley 10,000 to 12,000 feet in altitude, off the Callejon de Huaylas 250 miles north of Lima. Until 1957 the Vicos Indians were economically depressed serfs exploited by a long series of absentee landlords, but then they were freed by government proclamation.

The principal Vicos food crops are corn and potatoes; intake of animal proteins is negligible. Dietary surveys in 1952 and 1953 (*2*) and a check study in 1956, when the roentgenograms were taken, revealed that the average daily intake of vitamins A and B_2 and calcium were respectively 3, 56, and 14 percent of adjusted INCAP recommended allowances (*3*). Preliminary studies suggest that Vicos soils are calcium-deficient. Calorie and protein intake were about 70 percent of the recommendations, and fats represented only 7 percent of the daily caloric intake. Superposed on this inadequate nutrition was a heavy infestation of intestinal parasites, particularly *Ascaris* (*4*).

The posteroanterior roentgenograms of the left hand were taken by Humberto Mesones, through the courtesy of Ramon Vallenas, subdirector of Peru's Department of Industrial Hygiene. The roentgenographic technique, the developing procedure, and the photodensitometric apparatus used in the analysis have been described elsewhere (*5*) and need only brief mention. Eight- by ten-inch No-Screen film in cardboard holders was used, and an aluminum-zinc alloy film calibration wedge was simultaneously exposed with the subject's hand. The x-ray apparatus was a mobile Phillips 15 M A, manufactured in the Netherlands. Electric current was provided by a 220-v 60-cy/sec gasoline generator with a 3500-watt output. Exposure time was lengthened slightly to compensate for drawdown. The developed film was placed in the photodensitometric apparatus, and the middle phalanx of the fifth finger was evaluated for bone density coefficients at three sites or trace paths: the proximal and distal ends, whose values were averaged, and the centers. In this analysis the bone density coefficient is the number of grams of the aluminum-zinc alloy which, in a similar geometric shape, would absorb the same amount of x-radiation as the bone, divided by the volume of bone in cubic centimeters.

The Quechua Indian means, grouped by age (Table 1), stand in decided contrast to a series of normal white boys drawn from various parts of the United States (*6*). The means for the 7–9- and 10–12-year-olds of both Indians and whites are similar, but then the 13–15- and 16–20-year-olds from the United States show increases statistically significant at the .001 level, or better, for both the phalanx end and center trace paths. No such increase is present in the Indian boys in the age groups studied. The mean differences between Indians and whites in the 13–15- and 16–20-year groups are also statistically significant at the .001 level for each trace path. Accordingly, bone mineralization shows steady mean increases through the teens in United States whites but none at all in the Indians.

Table 1. Mean density coefficients of the phalanx center and phalanx end trace paths of Vicos Indian boys and United States white boys.

Age group	Cases (No.)	Density coefficient (mean ± standard deviation)	
		Phalanx center	Phalanx end
91 Vicos boys			
7–9	18	0.98 ± 0.30	0.59 ± 0.16
10–12	29	1.06 ± 0.23	0.65 ± 0.15
13–15	31	1.02 ± 0.21	0.64 ± 0.14
16–20	8	0.99 ± 0.40	0.66 ± 0.25
624 United States white boys			
7–9	77	1.02 ± 0.23	0.64 ± 0.11
10–12	101	1.03 ± 0.28	0.66 ± 0.16
13–15	225	1.32 ± 0.30	0.89 ± 0.21
16–20	221	1.43 ± 0.24	1.03 ± 0.19

The lack of increased bone density through the late teens in the Vicos Indians is probably due to dietary inadequacies. This view is supported by Williams and associates (*7*), who observed that bone-density measurements reflected the nutritional history of an individual. In addition, radical decreases in dietary calcium in rats depress bone-density values of their femurs (*8*) and caudal vertebrae (*7*). While this suggests that the depressed bone density coefficients of the Vicos Indians may be a result of their low calcium intake, the marked deficiencies in other nutrients and the extreme parasite infestation must also be considered. At Vicos, augmented bone mineralization, indicated by higher density values, may occur in the early 20's although we have no roentgenograms of this age group. The higher standard deviations in the numerically inadequate 16–20-year-old group may presage such an increase in bone mineralization. Indeed, the chewing of coca by almost all the Vicos Indian men (but never by the women) may result in increased calcium ingestion, since release of the alkaloid in coca is accomplished by mixing *cal* with it. *Cal* is thought to contain considerable quantities of calcium and is the Spanish word for lime.

The depressed bone mineralization in the Vicos boys is paralleled by an average lag of several years in skeletal ma-

turation (*9*) when assessments of the same roentgenograms are compared with Greulich-Pyle (*10*) standards. This is the greatest retardation in skeletal maturation reported for a number of preadult Peruvian series (*11*). Furthermore, the Vicos Indian boys show a mean deceleration of growth from about 10 to 15 years of age compared with other series from the Peruvian Sierra. After 15 years of age, the Vicos boys show a belated growth spurt that may relate to puberty. The slow and retarded growth, maturation, and phalangeal mineralization of the Vicos boys and the ultimately small body size of the adult men (*12*) probably reflect body economy in utilizing the meager amount of available calcium, as well as an inadequate total nutritional environment.

Clearly, the photodensitometric analysis of bone mineralization fits in closely with the growth and maturational data and provides revealing information on the relationship of food to physique. After several years on a diet raised to adequate levels, the Vicos Indian boys will be restudied with respect to any alterations in their developmental patterns (*13*).

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Increased Ascorbic Oxidase Activity Induced by the Fungal Toxin, Victorin

The toxin theory of disease has been an intriguing concept ever since the discovery of diphtheria toxin in 1888, by Emile Roux and Alexandre Yersin. In the field of animal pathology, the theory has led to brilliant advances in the understanding and control of disease. The application of this concept to the field of plant pathology, although admittedly less fruitful, has in the last decade yielded important results.

The studies of Braun (*1*), Dimond and Waggoner (*2*), Gäumann (*3*), and Gottlieb (*4*), to mention a few, clearly demonstrate that plant pathogens are capable of producing metabolites in culture which, when they are applied to the host, produce injurious effects in some cases similar to those encountered in natural infection. However, proof that plant pathogens produce toxins which are directly and solely responsible for the symptoms found in infected plants is still lacking.

Victorin, the toxin produced by the fungus *Helminthosporium victoriae* M. and M., first described by Meehan and Murphy (*5*), offers a unique tool for investigation of the toxin theory in relation to plant disease. These workers, as well as Litzenburger (*6*) and Luke and Wheeler (*7*), observed that, unlike other phytotoxins which generally lack the host specificity exhibited by the pathogen involved, victorin affected only those varieties of oats that were susceptible to the fungus (hybrids derived from victoria). Luke and Wheeler (*7*) also demonstrated that high yields of toxin could be obtained from highly pathogenic isolates of the fungus, whereas nonpathogenic strains failed to produce toxin.

Studies by Romanko (*8*) disclosed that victorin caused three- to five-fold increases in respiration of oat tissues of varieties susceptible to *H. victoriae* but that it failed to produce any appreciable effect on the respiration of Camellia, a resistant variety. This was apparently the first report of a toxin's producing such an effect only in plants susceptible to the pathogen. Further studies carried out by me (*9*) have shown that this increase in respiration is directly proportional to the concentration of toxin applied (original culture filtrate, containing 1000 units per milliliter as measured by the method of Luke and Wheeler, diluted 2.5×10^{-2}) (Fig. 1).

When cuttings were placed in toxin for 4 hours and exposed to light, and the enzymatic activity was measured 12 hours later, ascorbic oxidase, the major terminal oxidase system found to be in operation in susceptible oats, was found to be four times as high as that in comparable tissues (Fig. 2). The possible reasons for this increase in enzyme activity are at present not known, but in view of Newcomb's (*10*) findings that auxin (indoleacetic acid) greatly increases ascorbic oxidase activity in tobacco pith cells grown in culture, the results obtained appear to be significant. Tests with oats of resistant varieties showed that treatment with the same concentration of victorin failed to produce any detectable effect on ascorbic oxidase activity.

Romanko's studies (*8*) suggested that the increase in respiration of susceptible tissues caused by victorin may be due to uncoupling of phosphorylation from oxidation. Studies with 2,4-dinitrophenol (DNP), a proven respiratory uncoupler,

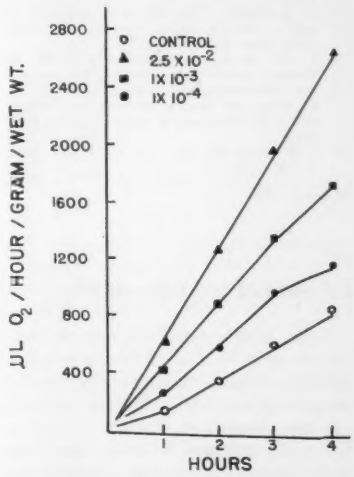

Fig. 1. Increase in respiration of susceptible oat tissue as a function of toxin concentration.

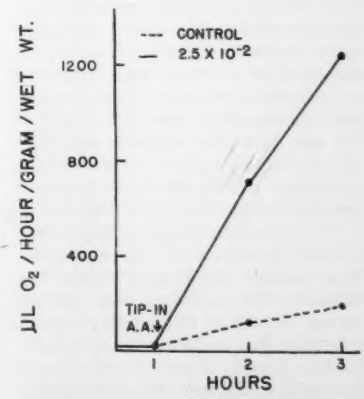

Fig. 2. Increase in ascorbic acid oxidase activity of homogenates from susceptible oat plants treated with victoria.

and victorin strongly indicate that both may have a similar mode of action. Susceptible tissues which have previously been exposed to victorin fail to respond to the addition of DNP. If victorin has an effect similar to that of DNP, it is probable that the rate-limiting phosphate acceptor systems are by-passed.

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31 March 1958

Crystallization of Chlorophylls

It has been pointed out that the successful crystallization of the chlorophyll pigments depends on high purity and the presence of water (*1*). We wish to report (*2*) the observation that the precipitation of the chlorophylls from highly impure extracts in organic solvents by washing with water constitutes a coprecipitation of *crystalline chlorophyll a* with amorphous chlorophyll *b*. This observation was made during a systematic spectrophotometric survey of each fraction obtained during the preparation of microcrystalline chlorophylls according to the method of Jacobs *et al.* (*1*). A sample of the petroleum ether extract of the pigments (see below) showed a pronounced absorption band with a peak at 745 mμ. According to Jacobs and Holt (*3*), this absorption band (corrected for scattering) is associated with a microcrystalline suspension of chlorophyll *a*.

The following example provides a generalized description of our procedure. Four pounds of fresh spinach was blended with acetone and filtered through a pad of Hyflo Super Cel on Whatman No. 1 filter paper in a large Büchner funnel. About 600 ml of solution passed through the filter before chlorophyll appeared. This solution, containing some of the yellow pigments and acetone soluble lipids, was discarded. After further acetone extraction of the gross content of the chlorophylls, the pigments were transferred in a separatory funnel to a single 500-ml portion of Skelly solvent F by successive treatment of 1-liter portions of the acetone extract with 2.5-liter portions of distilled water. Crystallization of chlorophyll *a* was already apparent in the petroleum ether after the second transfer from acetone (dashed curve of part A, Fig. 1). The solid curve of part A, Fig. 1, was obtained after all the pigments had been transferred to the petroleum ether. The dashed curve represents the spectrum of a 1:7.5 dilution with petroleum ether, while the solid curve represents the spectrum of a 1:30 dilution. The pigments were precipitated in the centrifuge and washed several times with fresh petroleum ether.

The separation of chlorophylls *a* and *b* was achieved at this point by the chromatographic procedure utilized by Jacobs *et al.* (*1*). The crystallization of the individual chlorophylls was accomplished in a manner somewhat similar to that used by these authors. The isopropyl alcohol–pentane solution of chlorophyll obtained as the effluent from the chromatographic column was thoroughly washed with water. During this procedure, microcrystals of chlorophyll *a* appeared as shown by the absorption spectrum (part B, Fig. 1). Chlorophyll *b* was removed from the sucrose adsorbent with acetone. This was followed by transfer of the chlorophyll *b* to petroleum ether by addition of water. Thorough water washing of the petroleum ether layer was continued until microcrystalline chlorophyll *b* appeared as shown by the absorption spectrum (part B, Fig. 1). Collection of the crystals was considerably simplified by the use of a model L Spinco ultracentrifuge (20,000 *g* for up to 30 minutes).

It should be remarked that all operations were carried out in a cold room at 4°C. Chromatography of the pigments at room temperature resulted in obvious color changes while the pigments were still on the sucrose adsorbent.

In addition to the spectrophotometric studies presented here, other physical studies of these crystals have been carried out (*4*). G. Donney of the Geophysical Laboratory of the Carnegie Institution of Washington took several x-ray powder diagrams of our crystalline preparations (*5*). It was found that the powder diagrams of the mixture of chlorophylls *a* and *b* precipitated from petroleum ether were identical with the powder diagrams of the pure chlorophyll *a* crystals. Such an observation has also been made with artificial mixtures of chlorophylls *a* and *b* (*6*). Since the spectrum of the redissolved precipitate shows the presence of chlorophyll *b*, this indicates that chlorophyll *b* in an amorphous form coprecipitates with the microcrystalline chlorophyll *a*. The less likely possibility that a mixed crystal with practically unchanged parameters is formed is not excluded by these considerations.

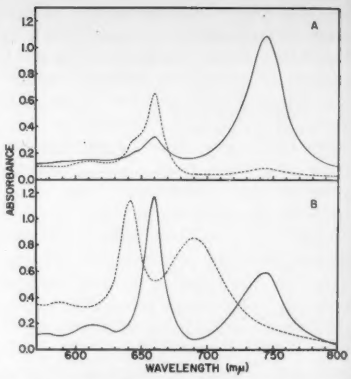

Fig. 1. Absorption spectra of precipitated chlorophylls in petroleum ether. *A*, Spectra of mixed chlorophylls at two stages of crystallization (see text). *B*, Spectra of pure chlorophyll *a* (solid curve) and chlorophyll *b* (dashed curve) showing absorption bands for both dissolved and microcrystalline chlorophylls. The spectra were obtained with a Cary model 14 spectrophotometer with a 1-cm cell; they have not been corrected for scattering.

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5. We wish to extend our thanks to Dr. Donney for making the x-ray powder diagrams. Dr. Donney will carry out an independent detailed analysis of the crystallographic structure of our chlorophyll *a* crystals. We also wish to thank Dr. I. Fankuchen of Brooklyn Polytechnic Institute for making a low-angle x-ray powder diagram of the chlorophyll *a* microcrystals.
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15 April 1958

Inhibition of Adrenal Steroid 11-Oxygenation in the Dog

Inhibition of adrenal cortical secretion by a direct action on steroid biosynthesis has been described following administration of amphenone B [3,3-di(*p*-aminophenyl)butanone-2 dihydrochloride], but limitations imposed by the toxic effects of this substance have led to the search for other inhibitory agents. Recently, the

compound 2-methyl-1,2-bis(3-pyridyl)-1-propanone (SU 4885) (*1*), has been synthesized by Allen and Bencze (*2*). This report is concerned with the action of this drug on adrenal cortical secretion in the dog.

Normal dogs were given an intravenous infusion of ACTH, and adrenal venous blood was obtained at timed intervals according to the method of Nelson and Hume (*3*). The plasma was extracted with chloroform and subjected to paper chromatography, according to the technique of Bush (*4*) and Zaffaroni (*5*). Identification was carried out by chromatographic and spectrophotometric means. In each case the free steroid ran on the Bush ("B 3" and "B 5") and Zaffaroni (toluene–propylene glycol) systems at identical rates with known steroid standards. Acetylation of each of these unknown compounds also resulted in acetates that moved at identical rates with known acetates of each. The presence of 17,21-dihydroxyketones was indicated by a positive Porter-Silber reaction (*6*) in the appropriate instances. Sulfuric acid spectra were in good agreement with those of appropriate standard compounds. All steroids isolated from adrenal venous blood gave, in addition, maximal absorption in ultraviolet light at 238 to 240 mμ, and the positive soda-fluorescence reaction of Bush (*4*) for Δ^4,3-ketones. Pregnane-3α,17α,21-triol-20-one (tetrahydro-S) was identified in the urine of a patient receiving the drug by negative reactions for Δ^4,-3-ketones, positive Porter-Silber and blue tetrazolium reactions, identical running rates both of the free and acetylated compound with those of authentic tetrahydro S and sulfuric acid spectra with absorption peaks at 315 and 410 mμ. Quantitative estimation was carried out by elution of the steroids off paper and application of the blue tetrazolium and Porter-Silber reactions. Total 17-hydroxycorticosteroids in blood were determined by the method of Nelson and Samuels (*7*).

A single intravenous injection of 75 mg of SU 4885 bitartrate per kilogram caused a decrease in adrenal venous 17-hydroxycorticosteroids to 10 percent of the initial value within 10 minutes followed by a return to 75 percent within 3 hours. The most notable effect, however, was seen when the individual steroids were identified. Figure 1*a* shows that Δ^4-pregnene-11β,17α,21-triol-3,-20-dione (cortisol) was reduced from an initial value of 6.0 μg/min to unmeasurable levels within 20 minutes and was only 1.2 μg/min 5 hours later. Simultaneously, Δ^4-pregnene-17α,21-diol-3,20-dione (Reichstein's compound S) appeared and rose steadily from previously undetectable levels to 5.6 μg/min at 5 hours, thereby accounting for the greater part of the 17-hydroxycorticoid secretion

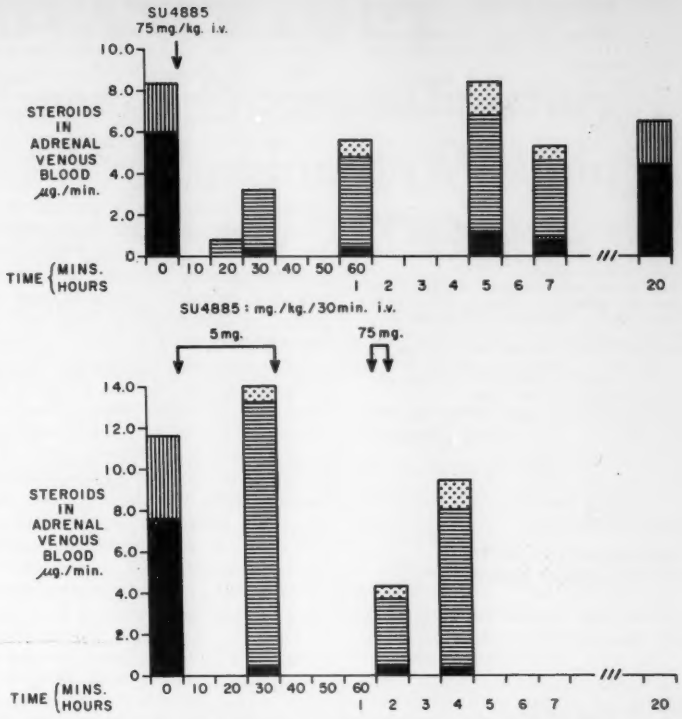

Fig. 1. (*a*) Effect of single injection of SU-4885 (75 mg/kg) on steroids in adrenal venous blood of a 19.3-kg dog. (*b*) Effect of 30-minute infusions of SU-4885 (5 mg and 75 mg/kg) on a 23-kg dog. Solid areas, cortisol; vertical lines, corticosterone; horizontal lines, 11-deoxycortisol (compound S); dotted areas, deoxycorticosterone.

at this time. Δ^4-Pregnene-11β,21-diol-3,-20-dione (corticosterone), which was present together with cortisol in the untreated animal, disappeared, and Δ^4-pregnene-21-ol,3,20-dione (deoxycorticosterone) was identified. The inhibition of 11-hydroxysteroids lasted for approximately 8 hours, and 20 hours after the injection, cortisol had returned to its initial value.

In further experiments the infusion of only 5 mg of the drug per kilogram over a period of 30 minutes produced no fall in total 17-hydroxycorticosteroids and, in fact, a rise was observed, but Fig. 1*b* shows that cortisol was reduced from 7.5 μg/min to 0.5 μg/min with the appearance of 12.5 μg of compound S. In contrast with these findings, amphenone hydrochloride, when injected in a dosage equivalent to 75 mg of SU 4885-bitartrate per kilogram, produced a temporary decrease in cortisol and corticosterone, both of which returned to 50 percent of the initial values in 2 hours, but without the appearance of 11-deoxy compounds, indicating that amphenone had no selective action on 11-oxygenation.

Preliminary clinical studies made on a patient suffering from Cushing's syndrome indicate that SU 4885 may have an action in man similar to that in the dog. The administration of the drug to this patient was followed by the appearance of large amounts of tetrahydro-S in the urine and was accompanied by a decreased excretion of tetrahydrocortisone and tetrahydrocortisol.

These experimental results demonstrate that SU 4885, in large doses, causes a generalized suppression of adrenal steroid biosynthesis which is followed by a more prolonged period during which 11-oxygenation is selectively inhibited. In smaller doses, the effect on total steroid secretion is not seen, but a profound inhibition of 11-oxygenation occurs, indicating that this particular enzyme system is especially sensitive to the drug. Similar results with this substance have recently been obtained by another group of investigators (*8*).

It is to be anticipated that a study of the relationship between the chemical structure of this substance and its mode of action may lead to the elaboration of further compounds capable of inhibiting adrenal enzyme systems (*9*).

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† Research fellow in medicine of the American College of Physicians, 1957–1958.
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14 May 1958

n-Butyl 5-Chloro-2-pyrimidoxyacetate—a Plant Growth Regulator Analog

Since the first demonstration of plant growth stimulation by substituted phenoxyacetic acids (*1*), much attention has been directed toward this series of compounds in an attempt to correlate the position and type of substituent with observed growth promotion. The results of the many investigations aimed at the elucidation of the mechanism of growth-regulator action have been resolved into three general theories.

One of these theories (*2*) supposes that there is a chemical reaction between the regulator and appropriate groups, probably nucleophilic, on some plant substrate, resulting in the formation of new convalent bonds. It has been shown that the most likely point of attack on the ring is at the positions *ortho* to the ether oxygen. Another theory (*3*) gives major importance to the shape of the regulator molecule and the specificity of its "fit" onto some receptor within the plant. In this case, the benzene nucleus with its substituents acts as a whole at the locus or point of attachment, and chemical reactions at the ring are considered unlikely. The third and most recent theory, unlike the other two, is not concerned with the relations of the regulator with an "active site," but suggests that the growth-regulating activity of a compound is primarily associated with its ability to chelate metal ions, such as Mg^{++} (*4*).

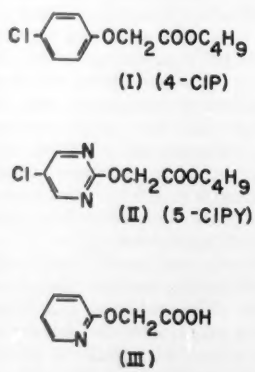

Fig. 1. Structural formulas.

In order to make a comparative test of these theories, we have prepared the butyl ester of 5-chloro-2-pyrimidoxyacetic acid (Fig. 1, II) (*5*). This compound is almost identical with the very active growth regulator, butyl *p*-chlorophenoxyacetate (Fig. 1, I) in its size, shape, ring planarity, molecular weight, halogen and ester reactivity, and also in those physical constants which were measured. However, the pyrimidine offers no possibility of nucleophilic reaction in the positions *ortho* to the ether oxygen (positions 1 and 3), and an aromatic type of substitution has never been observed to occur in positions 4 or 6 of the pyrimidine nucleus.

The plant growth regulatory activity of compounds I and II (Fig. 1) was measured by use of the oat coleoptile, wheat coleoptile, oat first-internode, and slit-pea curvature bioassays. In each case, the phenoxy ester was shown to be a highly active growth stimulator, while the pyrimidoxy ester was completely inactive.

An example of this difference in activity is shown in Fig. 2. For these tests, 4-mm sections of first internodes of dark-grown oat seedlings were rotated at *p*H 5.0 in citrate-phosphate buffer containing 2 percent sucrose and the compound under investigation at concentrations of 10^{-3} to $10^{-7}M$ (*6*). After about 20 hours, the oat sections were removed, their length was measured, and the data were subjected to statistical analysis. Results similar to those presented in Fig. 1 were obtained at *p*H 7.5 in 0.067*M* phosphate buffer, but were less clearly defined because of a diminished difference in growth between the treated sections and controls under alkaline conditions (*6*).

Consideration of the structure of compound II (Fig. 1) shows that it should be a chelating agent in the ways proposed for indole-3-acetic ester and for derivatives of phenoxyacetic acid. In addition, chelation could occur through the two nitrogens as it does in similar

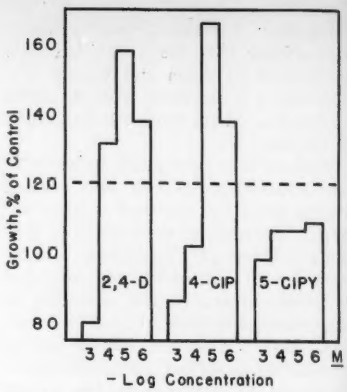

Fig. 2. Growth of oat first-internode sections at *p*H 5.0. Values above the broken line represent statistically significant promotion.

ureas and pyrimidines. Regarding the specificity of its "fit" onto a receptor, the molecule is spatially almost indistinguishable from that of compound I (Fig. 1) and while the pyrimidine ring would be expected to be more hydrophilic than the benzene ring, the recent descriptions of the high degree of plant growth stimulation by 2-pyridoxyacetic acid (Fig. 1, III) (*7*) indicate that lipophilic character may not be as important as previously suggested. Consequently, the inactivity of compound II (Fig. 1) does not substantiate two of the current theories, and it leads us to conclude that the *ortho* positions may indeed bear an important relation to biological activity in the phenoxy acid series (*8*).

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31 March 1958

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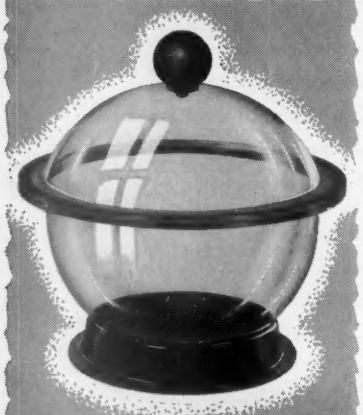

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The institute will try to answer the following questions. Can the work of public-health veterinarians be used in the many facets of a health department's nursing program? To what extent can veterinarians contribute to our still meager knowledge of radiation hazards? Can the fruits of veterinary research and the competencies of public-health veterinarians be applied effectively to human health fields as diverse as cancer, mental illness, heart disease, industrial hygiene, dental diseases, military medicine, geriatrics?

The institute will also feature separate sessions for five special committees which will meet with participants to discuss the most effective ways of utilizing career public-health veterinarians, private practitioners, regulatory officials, and industrial veterinarians in official and voluntary health programs. One of these committees will consider the entire field of education as related to the concept and practice of veterinary public health.

Small Angle X-ray Scattering

An International Conference on Small Angle X-ray Scattering from Metals will be held at Midwest Research Institute, Kansas City, Mo., 23–25 September. The program includes ten invited papers, to be given by W. W. Beeman of the University of Wisconsin; A. Guinier of the Conservatoire National des Arts et Métiers, Paris, France; A. Franks of the National Physical Laboratory, Teddington, England; R. Smoluchowski of Carnegie Institute of Technology, Pittsburgh, Pa.; V. Gerold and H. Fricke of the Max Planck Institut für Metallforschung, Stuttgart, Germany; J. C. Grosskreutz and F. R. Rollins of Midwest Research Institute; H. H. Atkinson of Cavendish Laboratory, Cambridge, England; R. E. Smallman, Atomic Energy Research Establishment, Harwell, England; J. S. Koehler, University of Illinois, Urbana; and A. Seeger of the Max Planck Institut für Metallforschung, Stuttgart, Germany. Approximately 40 other participants from laboratories in the United States and abroad will take part in the discussions.

Arrangements for the conference have been made by a committee under the chairmanship of J. C. Grosskreutz of Midwest Research Institute. Financial support is being provided by the National Science Foundation, the Office of Ordnance Research, the Office of Naval Research, the Wright Air Development Center of the U.S. Air Force, and Midwest Research Institute. The proceedings will be published as a special section of the *Journal of Applied Physics*.

International Submarine and Space Medicine Conference

An International Symposium on the Ecological Problems Related to Confinement in the True Submersible or Sealed Space Cabin will take place 8–12 September at the U.S. Naval Submarine Base, New London, Conn., under the auspices of the American Institute of Biological Sciences. The meeting is supported by the Advanced Research Project Agency of the Department of Defense.

This symposium, which is unclassified, will bring together international authorities in the field of submarine and space medicine for the purpose of integrating existing knowledge in these two closely related fields of research. It will be the first such international symposium. Foreign participants include: H. Laborit, Paris, France; O. Gauer, Kerckhoff Institute, Bad-Nauheim, Germany; R. Margaria, Physiological Institute, Milano, Italy; Pierre De Jours, Physiological Institute, University of Paris, France; A. Hurtado, Lima, Peru; C. M. Hesser, Karolinska Institute, Stockholm, Sweden; H. Taylor, Royal Naval Physiological Laboratory, Gosport, England; L. C. C. E. Pugh, London, England; F. Verzar, Basel, Switzerland; A. Aschoff, Max Planck Institute, Heidelberg, Germany; and Gunther Lehmann, Max Planck Institute, Dortmund, Germany.

African Geologists

The Association of African Geological Surveys, whose secretariat is in Paris (20, rue Monsieur), held its biennial meeting in Leopoldville (Belgian Congo) at the end of July under the chairmanship of F. Dixey, director of the Directorate of Overseas Geological Surveys in London. Seventy delegates represented 21 official geological surveys and 14 geological surveys belonging to the leading private companies in Africa.

New geological maps of Africa were presented in draft form at the congress. In addition, the program included a symposium on uranium in Africa. The

association established its future program, which included further work on the publication and revision of the geological maps. The association also plans to prepare a metallogenic map.

Vertebrate Speciation

A conference on vertebrate speciation will be held at the University of Texas, 27–31 October, as a part of the observance of the university's 75th anniversary. There will be five one-day sessions as follows: "Isolation Mechanisms," moderator, Ernst Mayr; "Evolution of Behavior," moderator, Lester Aronson; "Polymorphism and Polytypic Species," moderator, Lee R. Dice; "Population Dynamics," moderator, Charles M. Bogert; and "Age and Origin of Species," moderator, E. H. Colbert.

The last session will include three visitors from abroad: Gunnar Svardson, Institute of Freshwater Research, Drottningholm, Sweden; M. J. Littlejohn, University of Western Australia; and Curt Kosswig, University of Hamburg. For information, write to Prof. W. Frank Blair, Department of Zoology, University of Texas, Austin 12, Tex.

Forthcoming Events

September

23–25. Small Angle X-ray Scattering from Metals, intern. conf., Kansas City, Mo. (O. Fanning, Information Services, Midwest Research Inst., 425 Volker Blvd., Kansas City 10.

25–26. Effects of Pollution on Living Material, symp., London, England. (D. L. B. Copp, Inst. of Biology, 41 Queen's Gate, London S.D.7.)

26–6. International Council of Scientific Unions, 8th general assembly, Washington, D.C. (W. W. Atwood, Natl. Research Council–Natl. Acad. of Sciences, Washington, D.C.)

28–2. Electrochemical Soc., semiannual, Ottawa, Ontario, Canada. (R. K. Shannon, 1860 Broadway, New York 23.)

29–1. Analytical Chemistry in Nuclear Reactor Technology, 2nd conf., Gatlinburg, Tenn. (C. D. Susano, Oak Ridge Natl. Lab., P.O. Box Y, Oak Ridge, Tenn.)

October

1–8. Speleology, 2nd intern. cong., Bari, Lecce, and Salerno, Italy. (F. Anelli, Castellana-Grotte (Bari), Italy.)

2–3. American Soc. for Quality Control, 2nd chemical div. conf., Buffalo, N.Y. (J. E. Dillman, Hooker Chemical Corp., Niagara Falls, N.Y.)

2–5. International Soc. of Audiology, 4th cong., Padua, Italy. (M. Arslan, 37, via Altinate, Padua.)

2–6. International Soc. of Scientific Unions, 8th general assembly, Washington, D.C. (W. Atwood, Natl. Research Council–Natl. Acad. of Sciences, 2101 Constitution Ave., NW, Washington 25.)

4–8. Hydrology and Climatology, intern. cong., Lacco Ameno and Ischia, Italy. (Segreteria del Comitato Organizzatore, Congresso Internazionale di Idrologia e Climatologia, Viale Castrense, 9, Roma, Italia.)

4–13. International Federation of Agricultural Producers, 10th conf., Brussels, Belgium. (IFAP, 1624 Eye St., NW, Washington. D.C.)

5–8. American Inst. of Mining, Metallurgical, and Petroleum Engineers, fall, Houston, Tex. (E. O. Kirkendall, AIME, 29 W. 39 St., New York 18.)

6–9. Veterinary Public Health Practice, 1st inst., Ann Arbor, Mich. (H. E. Miller, Continued Education, School of Public Health, Univ. of Michigan, Ann Arbor.)

6–11. Electroencephalographic Study of the Higher Nervous Activity Processes in Animals and Man, colloquium (by invitation), Moscow, U.S.S.R. (Miss Mary A. B. Brazier, Massachusetts Neurophysiological Laboratory, Massachusetts General Hospital, Boston 14.)

7–9. Hypervelocity, 3rd symp., Chicago, Ill., (Air Force Office of Scientific Research, Air Research and Development Command, U.S. Air Force, Washington 25.)

7–9. International Soc. for the History of Pharmacy, cong., Venice, Italy. (A. F. Vitolo, Piazza Carrara 10, Pisa, Italy.)

8–12. Nutrition and Vital Substances,

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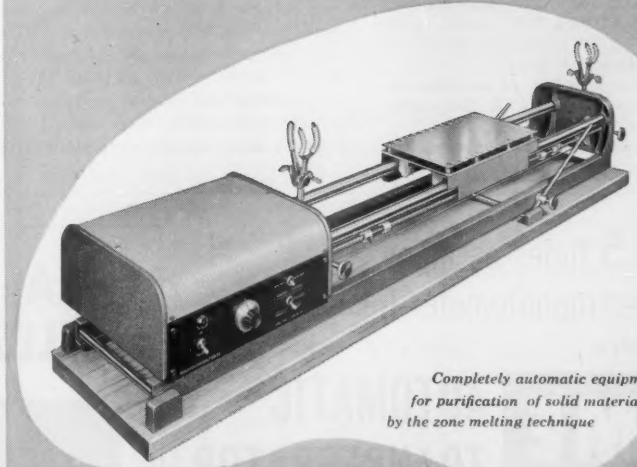

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4th intern. conv., Essen, Germany (Secretary General, Bemeroder Strasse 61, Hannover-Kirchrode, Germany.)

11–15. Salinity Problems in the Arid Zones, UNESCO symp., Tehran, Iran. (UNESCO, 19, avenue Kleber, Paris 16e, France.)

12–17. American Acad. of Ophthalmology and Otolaryngology, Chicago, Ill. (W. L. Benedict, 100 First Ave. Bldg., Rochester, Minn.)

13–15. Association of American Medical Colleges, 69th annual, Philadelphia, Pa. (W. Darley, AAMC, 2530 Ridge Ave., Evanston, Ill.)

13–15. National Electronics Conf., Chicago, Ill. (L. W. Von Tersch, Michigan State Univ., East Lansing.)

13–16. Society of Exploration Geophysicists, 28th annual intern., San Antonio, Tex. (C. C. Campbell, Box 1536, Tulsa 1, Okla.)

13–17. American Soc. of Civil Engineers, annual conv., New York, N.Y. (W. H. Wisely, ASCE, 33 West 39 St., New York 18.)

15–17. American Ceramics Soc., Glass Div., Bedford, Pa. (C. S. Pearce, 4055 N. High St., Columbus 14, Ohio.)

19–22. Land and Water, Soil Conservation Soc. of America, 13th annual, Asheville, N.C. (H. W. Pritchard, 838 Fifth Ave., Des Moines 14, Iowa.)

19–24. American Soc. of Anesthesiologists, Pittsburgh, Pa. (J. E. Remlinger, 802 Ashland Ave., Wilmette, Ill.)

(See issue of 15 August for comprehensive list)

Letters

Human Rights and Society

In T. Dobzhansky's article, "Evolution at work" [*Science* **127**, 1091 (1958)], which in general I found most interesting and instructive, there appears an incautious phrase or two which stands in need either of clarification or correction. I refer to his brief mention of the relation of biological to cultural evolution, wherein he makes the claims that "all men are equal in rights, but they are most certainly not biologically uniform," and that genetic diversity "does not make some of us superior and others inferior; no human being should ever be used as a means to an end" (*1*).

The first of these two claims as to the rights of man is rather obviously an assertion more easily stated than demonstrated, and the second claim runs head-on into some of the disturbing practicalities of man's sociocultural existence. I do not wish to belabor my point—in part because I do not believe my own and Dobzhansky's personal sympathies and orientations are too diverse. But there is need to call attention to the embarrassing and readily available evidence for the claims made: in all cultures to date, despite verbalizations at times to the contrary, men have not had equal rights, and the evidence would seem to indicate that it is rather dubious that such a state could ever be realized in human social affairs. The second claim, that no human being should ever be used as a means to an end, is an expression of an ideal that hardly takes into account the nature of man or of his social existence—past or present, or what conceivably might be realized in the future. Aside from the issue of claims such as these appearing in their unsubstantiated form, it is of interest to note that with such claims, I fear, Dobzhansky tends to place himself in the moral position occupied by Christianity. As Whitehead once said: "a sense of responsibility for the continuance of a social system is basic to any morality. Now this form of responsibility is almost entirely absent from Christianity. Jesus hardly mentions it, except for one or two remarks. . . . A society run on strictly Christian principles could not survive at all" (*2*).

C. W. Hartwig

Department of Economics and Sociology, Alabama Polytechnic Institute, Auburn

References

1. T. Dobzhansky, *Science* **127**, 1097 (1958).
2. L. Price, Ed., *Dialogues of Alfred North Whitehead* (Mentor, New York, 1954), p. 212.

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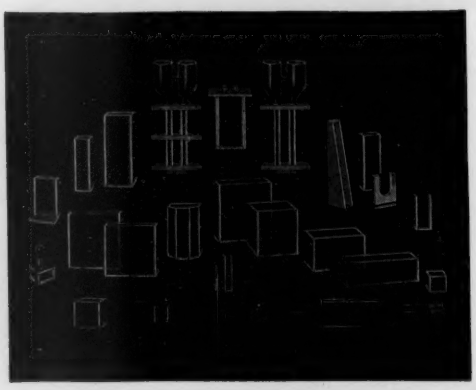

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Malignolipin

In this day, with biochemistry emerging as a highly complex and incompletely understood area of inquiry, it is particularly disconcerting to see publications in this field which jump to hasty and obviously unjustified conclusions.

I am thinking specifically of the report on malignolipin, by Kôsaki *et al.*, which appeared in the 16 May issue of *Science* [**127**, 1176 (1958)]. On the basis of the data presented (purely qualitatively), these authors report that malignolipin was isolated from every malignant tumor on which the extraction procedure was used, in greatest amounts from active tumors and in least amounts from necrotizing tumors. They further report that no malignolipin could be isolated from cattle brain or whole mouse bodies.

From these scanty data the five authors conclude that malignolipin is present in all malignant tumors, is not present in any other tissue, and is intimately connected with the malignancy of the tumors.

It seems almost needless to point out that until data on the percentage of recovery of malignolipin by the method used are presented, one cannot conclude that failure to isolate any from a tissue is indicative that none is present. The obvious suggestion to be deduced from the results of these authors is that the lipid may be associated with tissues of high growth rates. Yet, without investigating gonadal, regenerating, or embryonic tissue, the authors state that malignolipin is present only in the tumors. Obviously, considerably more facts must be presented before any such generalizations can be made.

STEVEN PRICE

Princeton, New Jersey

In the report published in the 16 May issue of *Science* [**127**, 1176 (1958)], I and my coworkers stated the existence of a new phospholipid in human malignant tumors and the nonexistence of such a lipid in normal tissues, such as cattle brain or whole bodies of normal mice, and we also mentioned the supposition that malignolipin is intimately related to the malignancy of tumor cells.

Fresh normal human tissues cannot be obtained in sufficiently large amounts to give conclusive evidence that such tissues do not contain malignolipin. Therefore we have attempted to detect malignolipin in the fresh whole bodies of normal mice, including of course gonadal tissues, and also in fresh cattle brain. Besides, we have attempted to isolate malignolipin from the stomach, brain, and liver of normal persons autopsied. In examination of these tissues no malignolipin could be detected.

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1. Shive, W., Snider, R. N., DuBilier B., Rude, J. C., Clark, Jr., G. E., and Ravel, J. O. Glutamine in Treatment of Peptic Ulcer. Texas State J. Med. *53*, 840-3 (1957).
2. Rogers, L. L. and Pelton, R. B. Glutamine in the Treatment of Alcoholism. Quart. J. Studies Alc. *18*, No. 4, 581–7 (1957).
3. Rogers, L. L. and Pelton, R. B. Effect of Glutamine on IQ Scores of Mentally Deficient Children. Texas Repts. Biol. and Med. *15*, No. 1, 84–90 (1957).
4. Tower, D. B. Nature and Extent of the Biochemical Lesion in Human Epileptogenic Cerebral Cortex. Neurology *5*, 113-30 (1955).
5. Meister, A. Metabolism of Glutamine. Physiol. Rev. *36*, 103–27 (1956).

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which is confined chiefly to small extracellular bodies in the tumors. In normal tissues, only sphingomyelin has the affinity for protoporphyrin (*1*). How to isolate the substance with the affinity for porphyrin from human malignant tumors, excluding sphingomyelin, constituted the basis of our discovery.

On the same basis, we originated a histological method for detecting malignolipin, excluding sphingomyelin, and ascertained that malignolipin could never be found in such tissues as normal liver, kidney, alimentary tract, lung, heart, pancreas, spleen, urinary bladder, and prostate, or in noncancerous tissues from individuals with hepatitis, liver cirrhosis, stomach ulcer, renal tuberculosis, and prostate hypertrophy, but could be found always in cancerous tissues. We studied one cancer of the esophagus, 12 stomach cancers, one cancer of the cecum, three cancers of the rectum, one uterine cancer, one renal adenoarcinoma, one Grawitz' tumor, one breast cancer, two urethral cancers, two seminomata, five cancers of the urinary bladder, one prostate cancer, one Hodgkin's malignant granuloma, and one reticulosarcoma (*2*).

No malignolipin could be detected histologically in human testicles, in tissues of 2- to 3-month human fetuses, or in chicken embryos of various stages of development (*3*).

Since malignolipin could be isolated from the blood and ascites of cancer-bearing plants as well as from Ehrlich's cancer ascites of mice, a sensitive method for exact detection of malignolipin in blood was devised. Tests, made in accordance with this method, of the blood of 18 normal persons and of eight patients not bearing malignant tumors were uniformly negative with respect to malignolipin, but tests were positive, without exception, for 25 patients bearing cancer. This method has been stated to be an excellent clinical method for the diagnosis of malignant tumors, especially for their early discovery (*2*).

Since malignolipin was thus supposed to be intimately related to the malignancy of tumor cells, its effect on the growth of Ehrlich's ascites cancer was examined to test the validity of this supposition and it was ascertained that malignolipin increased the intraperitoneal growth of Ehrlich's ascites cancer and the rate of mitosis of Ehrlich's ascites cancer cells (*2*).

TAKEKAZU KÔSAKI

Department of Biochemistry,
Mie Prefectural University
School of Medicine, Tsu, Japan

References and Notes

1. See reports No. 6 and 13 of the studies of T. Kôsaki *et al.* on the affinity of tissue elements for porphyrin, *J. Mie Med. Coll. (Japan)* 5, 29 (1955); 7, 313 (1957).
2. These results have been reported in *Proc. Japan Acad. No. 5* (1958).
3. A paper describing the particulars of these results is in preparation.

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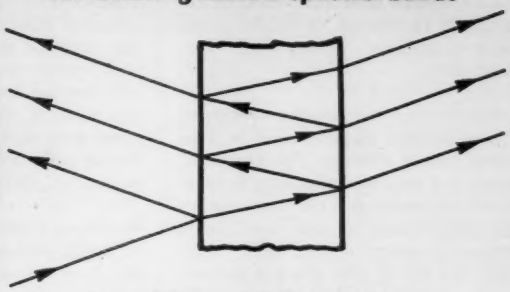

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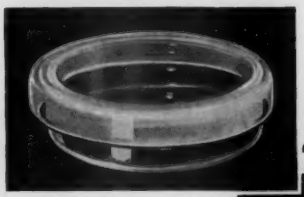

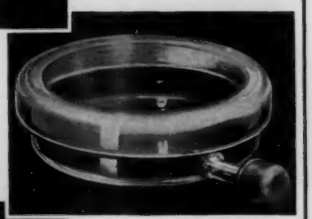

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■ TRANSISTOR-CHARACTERISTIC PLOTTER produces a family of curves on an auxiliary oscilloscope. The instrument furnishes collector currents up to 6 amp in continuous service, and up to 15 amp intermittently. Operation is entirely electronic, without blanking. Trace and retrace are shown, thus permitting observation of transistor hysteresis. (Dunn Engineering Associates, Inc., Dept. 309)

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JOSHUA STERN
National Bureau of Standards

PERSONNEL PLACEMENT

CLASSIFIED: 25¢ per word, minimum charge $4.25. Use of Box Number counts as 10 additional words. Payment in advance is required.

COPY for classified ads must reach SCIENCE 2 weeks before date of issue (Friday of every week).

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26 times in 1 year	**23.00 per inch**
52 times in 1 year	**22.00 per inch**

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Replies to blind ads should be addressed as follows:
Box (give number)
Science
1515 Massachusetts Ave., NW
Washington 5, D.C.

POSITIONS OPEN

(a) **Biochemist**; Ph.D. experienced hospital biochemistry; supervise section, act as liaison between laboratory, medical staff; fully approved 300-bed general hospital; large midwestern city. (b) **Bacteriologist**; modern, well-equipped county health laboratory; $5300 plus overtime; resort community 15,000; Northeast. (c) **Biochemist**; Ph.D. trained chromatography, steroid chemistry; cancer research; large general hospital; $7000; East. (d) **Bacteriologist**; congenial staff, modern laboratory facilities, 350-bed hospital; to $6000; Mideast. (e) **Pharmacologist**; Ph.D. for independent research in inflammation, analgesia and/or sympatholetic drugs; devise new screening methods, evaluate product; to $10,000; midwestern cosmetics concern. Woodward Medical Bureau, Ann Woodward, Director, 185 North Wabash, Chicago. X

Chief Medical Technologist to supervise clinical chemistry laboratory. B.S. and experience are minimum requirements. Contact Personnel Department, Cleveland Clinic Foundation, 2020 East 93 St., Cleveland 6, Ohio. X

POSITIONS OPEN

(a) **Assistant Director of Clinical Research**; preferably internist with teaching experience; duties consist of clinical investigation on new and improved products; one of leading pharmaceutical companies; East; $15,000 up. (b) **Project Leader** for supervision of 10 to 20 people in chemical analysis or instrumental analysis groups; research center of major food corporation in New York City suburb; preferably advanced degree in analytical, physical, or organic chemistry and 5 to 10 years' experience. (c) **Pharmacologist**, Ph.D., to conduct research independently in fields of inflammation, analgesia, or sympatholytic drugs; 14-year old company expanding into entire field of cosmetics and allied items; laboratory staff of over 125; opening also for Histochemist to conduct independent research; Ph.D. required; salaries up to $10,000; Midwest. S8-5 Medical Bureau, Burneice Larson, Director, 900 North Michigan Avenue, Chicago. X

Biochemist
Skin Physiologist, M.S., plus 5 years' experience in research in skin chemistry and physiology—knowledge of organic chemistry required.
Excellent professional environment and working conditions in new laboratories.
Liberal company benefits.
Send résumé in strict confidence to
D. M. DeHart
GILLETTE SAFETY RAZOR CO.
Gillette Park, Boston 6, Mass.

Experienced Histology Technician, ASCP registered preferred. Supervise histology laboratory in large midwestern teaching hospital, train technicians, opportunity for research. Box 163, SCIENCE. tf

NEW WORLD-WIDE GRADUATE AWARD DIRECTORY. First compilation ever prepared for American scientists, teachers, and librarians to subsidize their education and research in more than 350 universities in 45 states, 30 foreign lands. Stipends $200–$10,000. Complete information. Just published. Send $2 now. CRUSADE, Sci., Box 99, Station G, Brooklyn 22, N.Y. eow

POSITIONS OPEN

LIBRARY SCIENTIST

Mature person with biological-chemical training for key administrative position. Pharmaceutical industry experience preferable. Write stating qualifications and salary desired to

Wyeth Laboratories
Box 8299
Philadelphia 1, Pa.

Microbiologist. With a major in biochemistry and/or genetics for postdoctorate position at large western university. Send complete résumé with initial letter. Reply to Box 203, SCIENCE. X

Physical Chemist

An expanding Midwest pharmaceutical company needs a Ph.D. physical chemist with microbiological training to do research on paper chromatography and antibiotics assay. Write, stating background and experience to:

Technical Employment Coordinator
THE UPJOHN COMPANY
Kalamazoo, Michigan

SCIENCE TEACHERS, LIBRARIANS, ADMINISTRATORS urgently needed for positions in many states and foreign lands. Monthly non-fee placement journal since 1952 gives complete job data, salaries. Members' qualifications and vacancies listed free. 1 issue, $1.00. Yearly (12 issues) membership, $5.00. CRUSADE, SCI., Box 99, Station G, Brooklyn 22, N.Y. ew

POSITIONS OPEN

Ph.D. in Biological Science, recent or expected, research in pharmacology; ethical drug company, New York; good opportunity for man preferring small organization; $6500 to $7500. Box 202, SCIENCE. 9/5

COLLEGE TEXTBOOK FIELD EDITOR

Man with publishing experience as a college traveller who is willing to travel extensively during at least 6 months of the year, balance of year will be spent in the New York office.

Field work will consist of editorial procurement and related activities —office time will be devoted to editorial and textbook promotion responsibilities. Close familiarity with colleges and educational patterns in physical and biological sciences and engineering essential.

All replies confidential, write

REINHOLD TEXTBOOK DEPARTMENT
430 Park Ave., New York 22, N.Y.

Plant Pathologist

The Rohm & Haas Company has a position available for a plant pathologist with some training and experience beyond the Ph.D. He should be capable of assuming responsibility for directing the work of a small group of scientists and technicians in carrying out a research and development program involving laboratory, greenhouse and field tests. He will be called upon to devise meaningful screening tests for the fungicidal activity of candidate compounds submitted by the synthetic laboratories and to organize an effective evaluation program to find new and improved fungicides.

Complete laboratory and greenhouse facilities are maintained at Rohm & Haas Company's Bristol, Pa., plant with an experimental farm nearby. The plant is located in historic Bucks County, Pa., where excellent residential areas are readily accessible in the northern suburbs of Philadelphia or in the small communities of southern New Jersey.

Your reply should include information about your training, experience, and salary desired. All inquiries will be acknowledged, and treated confidentially.

Rohm & Haas Company
Office of Technical Employment
5000 Richmond Street
Bridesburg (Philadelphia) 37, Pa.

POSITIONS OPEN

UNIVERSITY OF ALBERTA HOSPITAL
EDMONTON, ALBERTA, CANADA

Applications are invited for the position of **Assistant Director of the Department of Clinical Laboratory Services.** The duties will be concerned with the future development of the biochemistry laboratory service in the hospital, consulting and advising on clinical problems and research projects involving biochemistry and teaching. A teaching appointment in the University of Alberta Medical School, while not automatic with this appointment, is customary. There will be ample opportunity to carry on individual research. The qualifications required are a degree in medicine and special training and experience in biochemistry. Preference will be given to those holding the M.R.C.P. or F.R.C.P. or a doctorate degree in biochemistry. Male, age 30–40 preferred but not essential. Salary $10,000–$12,000 per annum.

Interested parties should apply to the Medical Superintendent, University of Alberta Hospital, giving full details and the names of two references. X

POSITIONS OPEN

Senior Research Pharmacologist. Excellent opportunity exists for young Ph.D. with industrial experience in small, progressive pharmaceutical firm in upstate New York. Have a leading part in exciting and varied research program. Prefer man with cardiovascular and/or gastrointestinal interests. Excellent salary and fringe benefits. Inquiries will be held confidential. Send full information to Box 200, SCIENCE. 8/29, 9/5

POSITIONS WANTED

Bacteriologist: M.Sc., desires to relocate in western or southwestern part of country. Teaching and industrial research experience; 7 years with present firm; experience in chemotherapy. Box 204, SCIENCE. X

Pharmacologist: B.S. (biology major; chemistry minor); M.S. (neuroanatomy major; biochemistry minor); Ph.D. (pharmacology major); now on faculty, pharmacology department, large university. Medical Bureau, Burneice Larson, Director, 900 North Michigan, Chicago. X

USE THIS EASY SELF-MAILER to obtain further information

29 August 1958

Readers' Service

Information Requisition

It's Simple: Mark—Clip—Fold—Mail—No stamp required

This coupon is for your convenience—to facilitate your requests for further information about advertised products and items in Equipment News.

From:

Name .... **Position** .....

Company .....

Street .....

City ..... **Zone** .... **State** .....
(Please print or type)

Mark, clip coupon — FOLD HERE along this line — mail

Postage Will be Paid by Addressee

No Postage Stamp Necessary If Mailed in the United States

BUSINESS REPLY CARD
First Class Permit #12711 New York, N.Y.

Readers' Service

To: SCIENCE MAGAZINE
Room 740
11 West 42 Street
New York 36, New York

Fasten Here Only
Staple, Tape, Glue

The Market Place

BOOKS • SERVICES • SUPPLIES • EQUIPMENT

DISPLAY: Rates listed below—no charge for Box number. Monthly invoices will be sent on a charge account basis — provided that satisfactory credit is established.

Single insertion	$26.00 per inch
13 times in 1 year	24.00 per inch
26 times in 1 year	23.00 per inch
52 times in 1 year	22.00 per inch

For PROOFS on display ads, copy must reach SCIENCE 4 weeks before date of issue (Friday of every week).

SUPPLIES AND EQUIPMENT

ALBINO RATS
SWISS MICE
Price lists on request
DAN ROLFSMEYER CO.
Ph. ALpine 6-6149
Route 3, Syene Road, Madison, Wisconsin

SWISS MICE
BACTERIOLOGICAL AND GROSS TISSUE STUDY TECHNIQUES USED IN OUR QUALITY CONTROL
HUNTINGDON FARMS, INC.
2548 NORTH 27th ST. PHILA. 32, PA.

"OUR PREVIOUS AD

created a great deal of interest, for which we are grateful. Additional advertising in your magazine is contemplated."

SUPPLIES AND EQUIPMENT

Sprague-Dawley, Inc.
Pioneers in the development of the standard laboratory rat.
Sprague-Dawley, Inc.
P.O. Box 2071, Madison 5, Wisconsin
Phone: CEdar 3-5318

WHITE MICE
Guinea Pigs and Rats
J. E. STOCKER Box 4 Ramsey, N.J.

PROFESSIONAL SERVICES

Histology
for
Industry and Research
George L. Rozsa, M.D.
143 Linwood Ave. Buffalo 9, New York

BOOKS AND MAGAZINES

Your sets and files of scientific journals

are needed by our library and institutional customers. Please send us lists and description of periodical files you are willing to sell at high market prices. Write Dept. A3S, CANNER'S, Inc. Boston 20, Massachusetts

SCIENTIFIC JOURNALS WANTED

Sets, Runs and Volumes bought at top prices. Your wants supplied from our Back Files of over 3,000,000 periodicals. Abrahams Magazine Service; N. Y. 3, N. Y.

ADVANCES IN EXPERIMENTAL CARIES RESEARCH

Editor: Reidar F. Sognnaes
Price $6.75; AAAS Members' prepaid order price $5.75
246 pp., 49 illus., index, clothbound, 1955

This is the first monograph specifically devoted to data from the experimental production and prevention of tooth decay in laboratory animals. Twenty distinguished investigators, representing dentistry and allied basic sciences, report and review their researches. Unusually well organized, the book represents a coherent sequence, and is skillfully summarized by the editor in a final chapter, followed by very detailed subject and author indexes.

AAAS
1515 Massachusetts Avenue, NW
Washington 5, D.C.

29 August 1958

Readers' Service

Information Requisition

Use this easy self-mailer to obtain further information about items or literature from the Equipment section as well as from advertised products.

EQUIPMENT

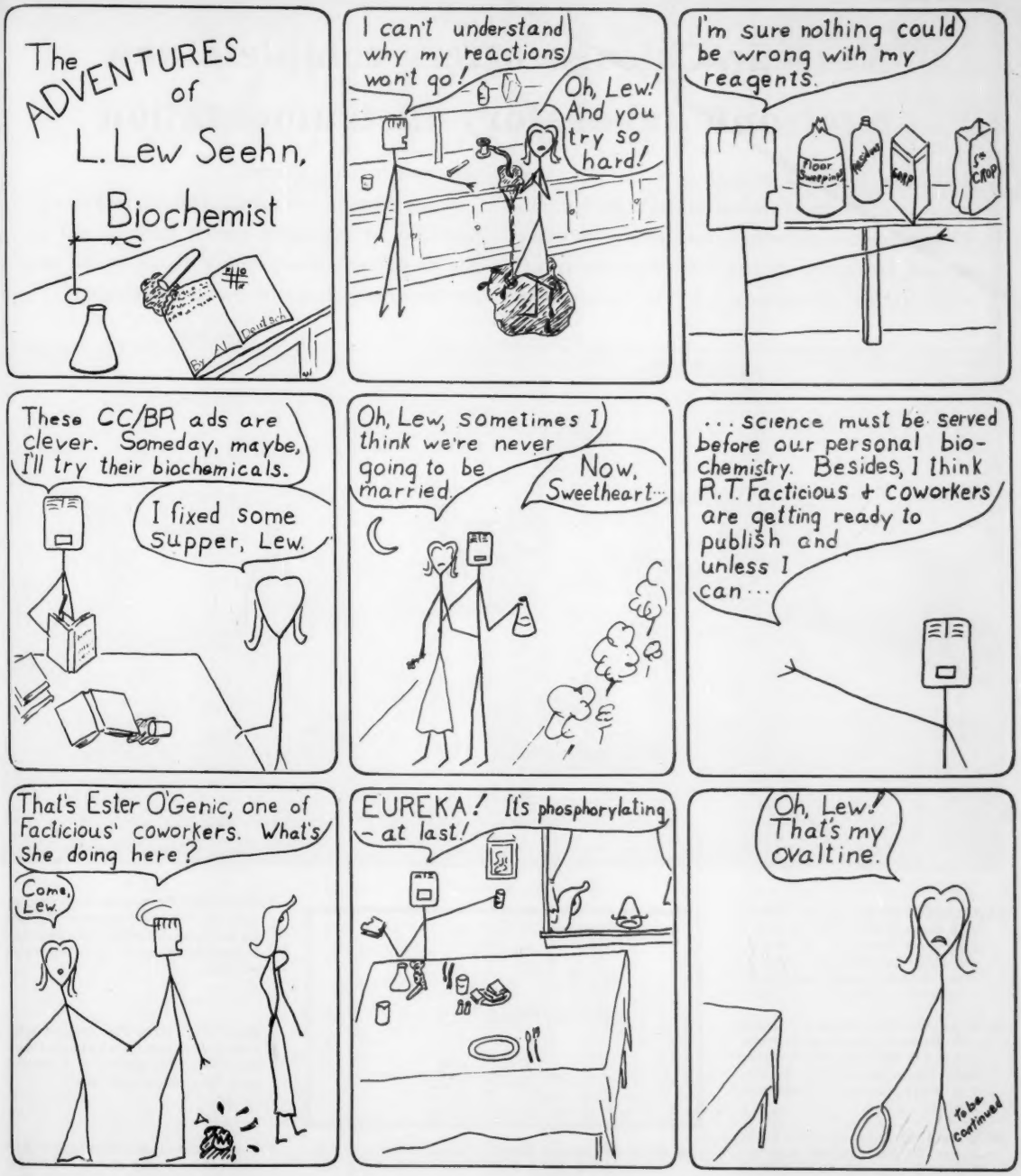
Circle below desired number corresponding to:

259 284 286 288 289 290 291 293
297 298 300 305 308 309

ADVERTISERS IN THIS ISSUE

In list below, check page number of advertiser from whom you would like more information. If more than one item appears in ad, letters (A, B, C) are used to indicate particular items available in order of appearance in advertisement. Where more than one ad appears on page, **"U" indicates upper ad, "L" lower ad, "I" inside ad, "M" middle ad,** and **"O" outside ad.** Advertisements in Personnel Placement and Market Place are not keyed. A multiplicity of items is indicated by *. Readers are requested to specify on this coupon the particular item in which they are interested; otherwise, the request cannot be processed.

☐ 438	☐ 439	☐ 440	☐ 441	☐ 442
☐ 444	☐ 482	☐ 483	☐ 484, LO	☐ 484, LI
☐ 485	☐ 486, UO	☐ 487, UI*	☐ 487, UO	☐ 487, LO
☐ 491	☐ 492			


The ADVENTURES of L. Lew Seehn, Biochemist
I can't understand why my reactions won't go!
Oh, Lew! And you try so hard!
I'm sure nothing could be wrong with my reagents.
These CC/BR ads are clever. Someday, maybe, I'll try their biochemicals.
I fixed some supper, Lew.
Oh, Lew, sometimes I think we're never going to be married.
Now, Sweetheart...
... science must be served before our personal biochemistry. Besides, I think R.T. Facticious & coworkers are getting ready to publish and unless I can...
That's Ester O'Genic, one of Facticious' coworkers. What's she doing here?
Come, Lew.
EUREKA! It's phosphorylating - at last!
Oh, Lew! That's my ovaltine.
To be continued

Dear Reader:

Please don't make Lew's mistake. Now, while you're thinking of it, take your trusty CC/BR Catalog in hand and order all your biochemicals from Calif. Corp.

P.S. If you don't have a Catalog, write for one today.

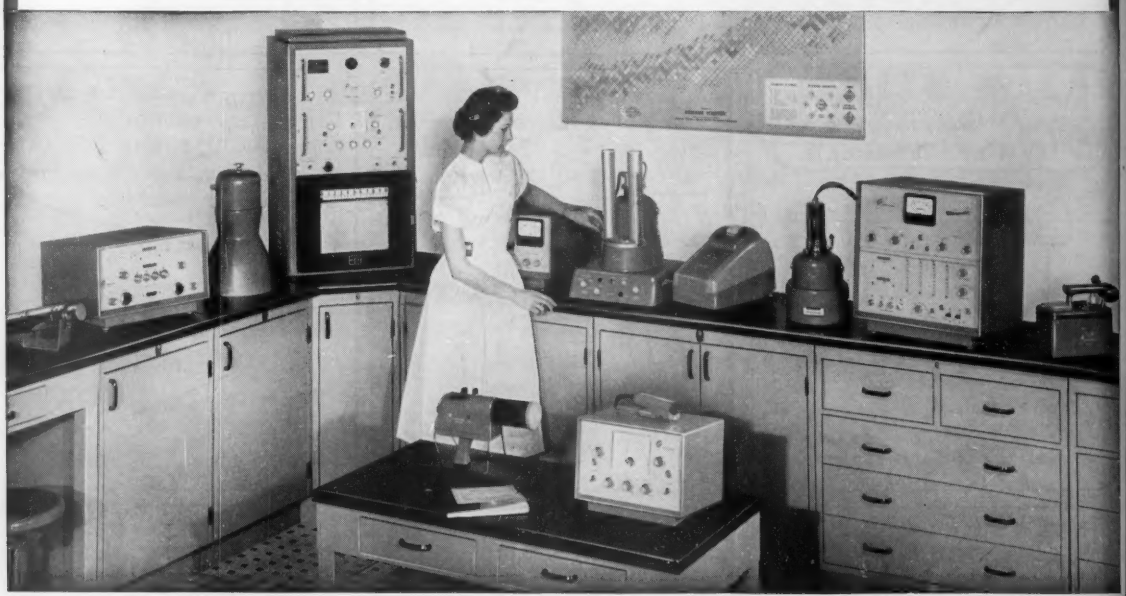
CALIFORNIA CORPORATION FOR BIOCHEMICAL RESEARCH

CALL COLLECT ANgelus 3-6741 CABLE: CALBIOCHEM
3625 MEDFORD STREET • LOS ANGELES 63, CALIFORNIA

Nuclear-Chicago offers complete new nucleonic laboratory instrumentation

More than two years' research went into the 33 *all new* instruments that have been added to the Nuclear-Chicago line now offered to the small or large nucleonic research laboratory. Among these high-quality advance-design instruments are many completely automatic counting systems.

Whether you are just starting a modest radioisotope laboratory or expanding present facilities, call on Nuclear-Chicago. For complete details on the new Nuclear-Chicago line, write for our new Catalog "Q".



1A Model DS5-3P Scintillation Detector with exposed 2" x 2" sodium iodide crystal and **1B** Model 132 Analyzer Computer for precision gamma-ray measurements using pulse-height discrimination techniques.

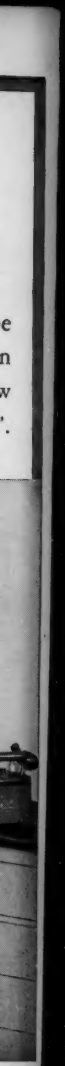
2A Model DS5-5 Scintillation Well Counter with exclusive "scaler-spectrometer" circuit and **2B** Model 1820 Recording Spectrometer for automatic quantitative energy separation of gamma-ray spectra.

3A Model 183B Count-O-Matic Binary Scaler, **3B** Model C110B Automatic Sample Changer with Model D47 Gas Flow Counter, and **3C** Model C111B Printing Timer for completely automatic changing, counting, and recording of as many as 35 soft beta emitting radioactive samples.

4A Model 3054 Manual Sample Changer with Model DS5 Scintillation Detector which features interchangeable alpha, beta, or gamma sensitive crystals connected to Nuclear-Chicago's finest scaler, the **4B** Model 192A Ultrascaler. Model 192A features decade scale of 10,000, one millivolt sensitivity, and precision automatic circuitry.

5 Model 2612P Portable Survey Meter contains a 1.4 mg/cm² thin window G-M tube for surveying for alpha, beta, or gamma contamination up to 20 milliroentgens per hour.

6 Model 2586 "Cutie Pie" features interchangeable ionization chambers for measuring beta, gamma, or x-radiation up to 250 roentgens per hour.

7 Model 1620A-S Analytical Count Rate Meter offers a wide choice of full scale ranges, four time constants, wide range high voltage supply. It is shown with a Model D34 thin window G-M tube and P11 probe for continuous monitoring or analytical radioactivity determinations.

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